Catalytic applicability of NNS and SNS ligand derived air-stable Ru complexes towards de(hydrogenative) construction of carbon-carbon and carbon-nitrogen bond

A Dissertation

Submitted in partial fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

by

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INDIA, September, 2021

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Dedicated

to

My Parents

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INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

Guwahati, Assam-781039, INDIA

STATEMENT

I, hereby declared that the work comprised in this thesis entitled "***Catalytic applicability of NNS and SNS ligand derived air-stable Ru complexes towards de(hydrogenative) construction of carbon-carbon and carbon-nitrogen bond***" is the outcome of the research work carried out by me under the supervision of **Dr. Dipankar Srimani, Department of Chemistry, Indian Institute of Technology Guwahati, India**, for the award of the degree of Doctor of Philosophy.

In harmony with the general practice of reporting scientific observations, due acknowledgements have been made if the work is established on the findings of other investigators.

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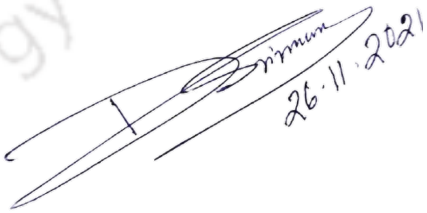
CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"*Catalytic applicability of NNS and SNS ligand derived air-stable Ru complexes towards de(hydrogenative) construction of carbon-carbon and carbon-nitrogen bond*"** which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by **Miss. Nandita Biswas** (Roll No: **166122001**) was carried out by her under my supervision at this institute. The work presented in her thesis is original and that has not been submitted elsewhere for a degree.



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As, I write my thesis during a worldwide pandemic (COVID-19) situation, I would also like to include all the professional and scientists that battle in the front line and risk their lives.

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-Nandita

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Contents

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Abbreviation

Ac	Acetyl
α	Alpha
Å	Angstrom
Ar	Argon
ACN	Acetonitrile
AD	Acceptorless dehydrogenation
ADC	Acceptorless dehydrogenative coupling
br.	Broad
bi pyridine	2,2′-bipyridine
β	Beta
Bn	Benzyl
Bu	Butyl
BH	Borrowing hydrogen
CCDC	Cambridge crystallographic data centre
COD	1,5-Cyclooctadiene
$CDCl_3$	Chloroform-d
Cy	Cyclohexyl
Cat	Catalyst
^oC	Degree Celsius
d	Doublet or day
dd	Doublet of doublet
δ	Chemical shift or delta
DA	Donor-acceptor
DCE	Dichloroethane
DCM	Dichloromethane
DFT	Density functional theory
DMSO	Dimethylsulfoxide
DMF	Dimethylformamide
DMA	Dimethylacetamide
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
EtOAc	Ethyl acetate
equiv.	Equivalent
ESI	Electrospray ionization
Et	Ethyl
EWG	Electron withdrawing group
EDG	Electron donating group

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g	Grams
γ	Gamma
HA	Hydrogen-autotransfer
h	Hours
HRMS	High resolution mass spectrometry
Hz	Hertz
MHz	Mega Hertz
i	Iso
FT-IR	Fourier transform infrared spectroscopy
J	Coupling constant
m	Multiplet
m	*Meta*
Me	Methyl
mg	Milligram
mL	Millilitre
mmol	Millimole
Mp	Melting point
MS	Molecular seive
MLC	Metal-ligand cooperation
NMR	Nuclear magnetic resonance
Ts	Tosylate
o	*Ortho*
ω	Omega
ORTEP	Oak ridge thermal ellipsoid plot program
p	*Para*
Ph	Phenyl
Py	Pyridine
Pr	propyl
PNP	2,6-bis-(di-*tert*-butylphosphinomethyl)pyridine
ppm	Parts per million
q	Quartet
rt	Room temperature
s	Singlet
THF	Tetrahydrofuran
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
t	*Tert*
TMS	Tetramethylsilane
TS	Transition state
XRD	X-ray diffraction

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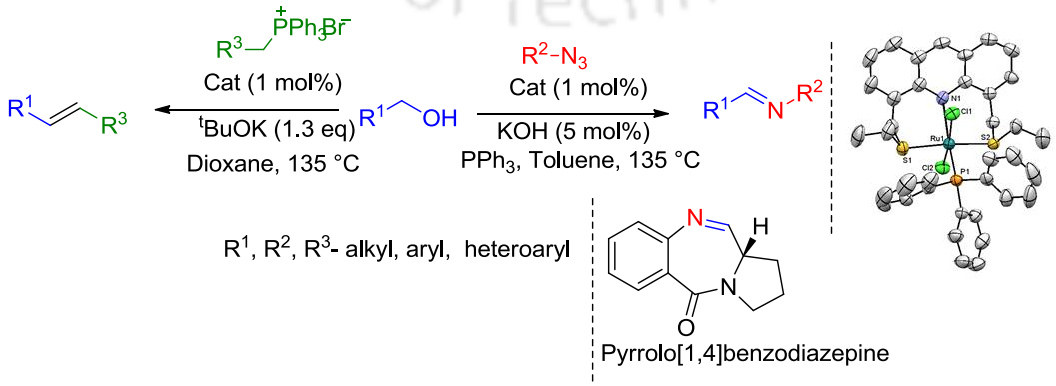
Abstract

The contents of the present thesis entitled as "***Catalytic applicability of NNS and SNS ligand derived air-stable Ru complexes towards (de)hydrogenative construction of carbon-carbon and carbon-nitrogen bond***" have been divided into five chapters based on the results achieved from the experimental works performed during the entire course of the PhD research programme.

Chapter 1 contains a brief introduction about the literature review of acceptorless dehydrogenative and borrowing hydrogen reactions of alcohols *via* homogeneous catalysis. Each of these chapters (**Chapter 2- Chapter 4**) contains an introduction, previous reported works, present results and discussion, an experimental section, and references, along with characterization data of products including spectral data. Overall, this thesis demonstrates some new and efficient approaches for the synthesis of different functionalized target compounds.

Chapter 2 highlights for the synthesis and characterisation of of NNS and SNS ligand derived air stable-Ru pincer complexes and investigated their catalytic applicability towards dehydrogenative aza-Wittig and Wittig reactions for the construction of C=N and C=C bonds. This protocol was also used for the synthesis of pyrrolo[1,4] benzodiazepines derivatives as they are important class of compounds having useful biological activity. The scope of this reaction is quite broad for different substrates such as alkyl, aryl as well as heterocyclic moieties.



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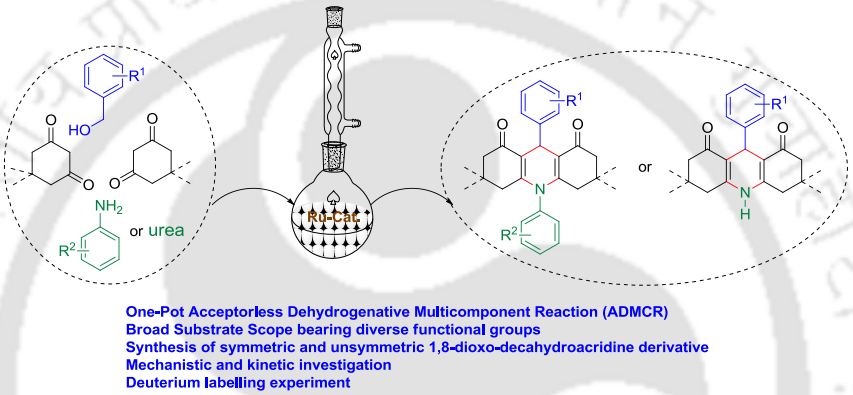
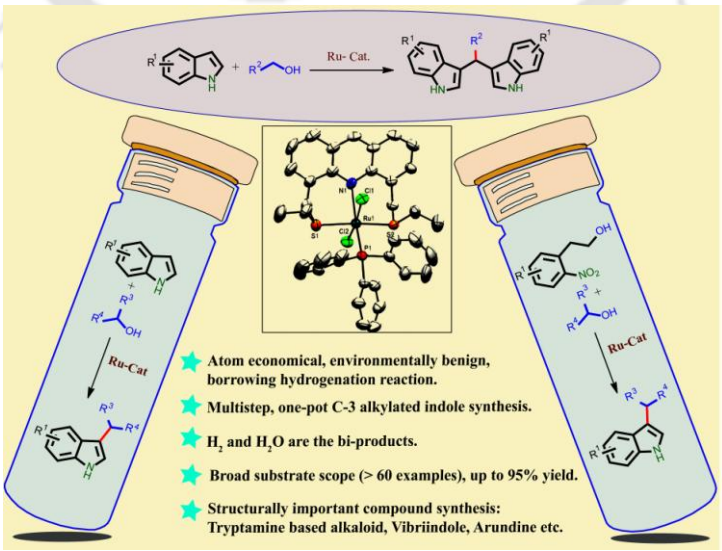
Chapter 3 demonstrates an efficient and atom-economic method for the facile synthesis of 1,8-Dioxo-decahydroacridine derivatives via Ru-catalyzed acceptorless dehydrogenative multicomponent reaction. This protocol is quite general to access the desire products in a wide range of substrates with good to excellent yields. In addition, mechanistic and kinetic studies were performed to understand the plausible reaction pathway involved for the target product formation which is discussed in this section in details. A time-dependent product distribution experiment is also presented and the reaction scale-up is performed to highlight the practical utility of this strategy.



Chapter 4 describes selective synthesis of C-3 alkylated of 1H-indoles with various aliphatic primary and secondary alcohols including cyclic alcohols as well as benzylic alcohols.



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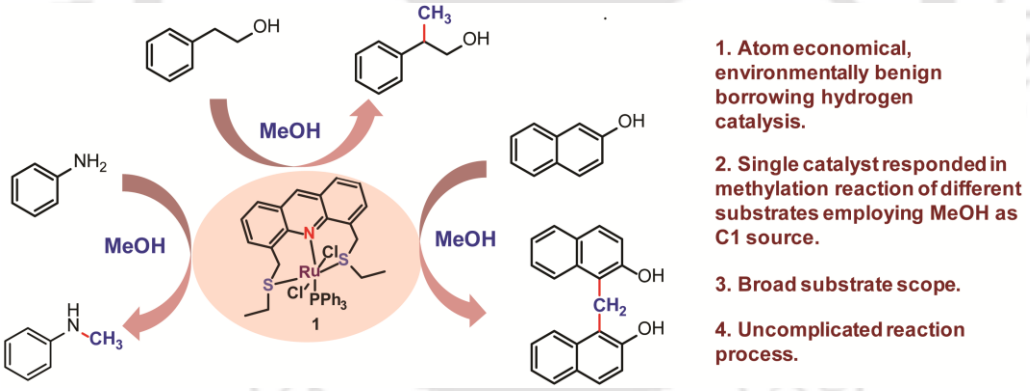
The selective synthesis of bisindolylmethane derivatives is also achieved from the same set of indole and alcohol just by altering the reaction parameters. Furthermore, the sustainable synthesis of C-3 alkylated indoles directly from 2-(2-. nitrophenyl)ethan-1-ol and alcohols catalysed by a Ru-complex via "borrowing hydrogen" strategy is reported. This protocol provides an atom-economical sustainable route to access structurally important compounds like arundine, vibrindole A and tryptamine based derivatives.

Chapter 5 represented the activity of acridine derived SNS-Ru pincer for the activation of methanol to apply it as a C1 building block towards *β*-C(sp3)-methylation reaction of 2-phenylethanols to provide good to excellent yields of the methylated products. Furthermore, mechanistic details, kinetic progress and temperature dependent product distribution of the reaction have been showed. To establish the environmental benefit of this reaction, green chemistry metrics have been reported. In addition, dimerization of 2-Naphthol *via* methylene linkage and formation of *N*-methylation of amine are also described in this study which offers a wide range of substrate scope with good to excellent yield.



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Chapter 1

Acceptorless Dehydrogenative and Borrowing Hydrogen Reactions of Alcohols via Homogeneous Catalysis

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1.1. Introduction:

The growing concern about sustainable use of natural resources and environmental pollution has prompted scientists to develop new synthetic strategies to fulfil human needs. In organic synthesis, it is important to synthesize useful building blocks through carbon-carbon and carbon-heteroatom bond formation and functionalization of a suitable atom to different functional groups. According to green chemistry principle[1], it is important to invent new reactions, which can lessen environmental impact by minimizing waste generation and increase atom economy. This concept urges chemists to develop new methodologies to produce sustainable chemicals and important building blocks from renewable resources. In this regard, catalysis reaction offers a great advantage in terms of energy efficiency, sustainability by increasing selectivity. The recent discovery of molecular catalytic dehydrogenation strategies opens up new possibilities for using organic molecules as a safe, storable, and transportable medium. Furthermore, catalytic dehydrogenation of renewable chemical feedstocks with the release of molecular hydrogen provides a new path in modern science by allowing direct access to plentiful organic substrates, with several practical uses in chemical synthesis and energy storage. So, in this context, the acceptorless dehydrogenative coupling (ADC) reaction and borrowing hydrogen (BH) catalysis are the extremely powerful approaches to synthesize a diverse range of useful organic building blocks *via* homogeneous catalysis.

1.2. Acceptorless dehydrogenation:

Acceptorless dehydrogenation (AD) reaction[2] can result not only easy removal of hydrogen molecule from substrate but also extremely efficient and environmentally benign approach for synthesizing valuable products. The advantage lies in acceptorless dehydrogenation (AD) reaction is that it eliminates the stoichiometric amount of waste generation, which occurs during conventional oxidation process. The removal of hydrogen atoms from the neighbouring atomic location of an organic substrate is endergonic and making this process thermodynamically disfavoured. Conventionally,

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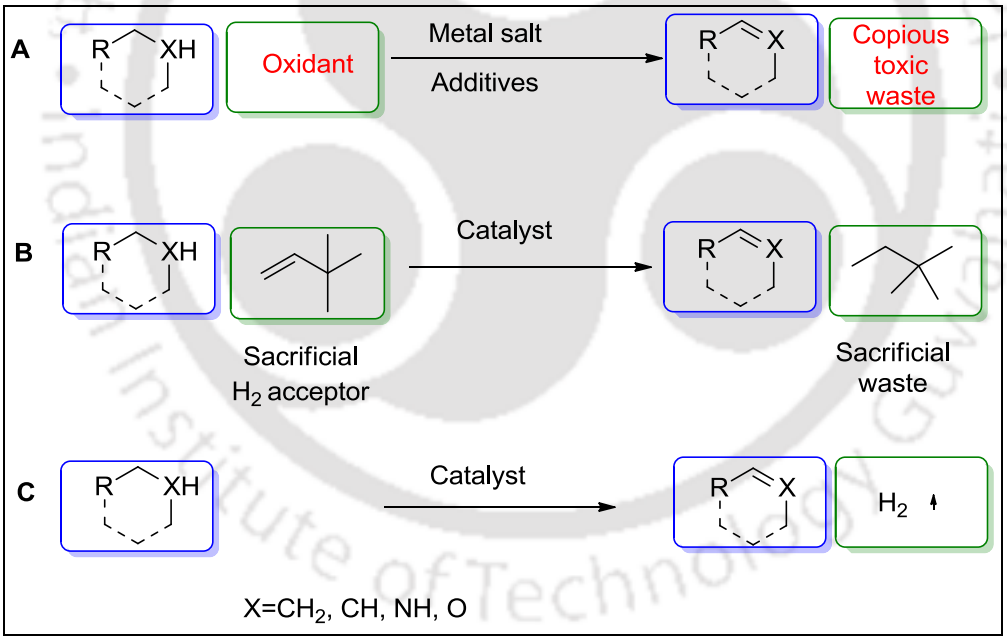
inorganic oxidants such as dichromate,[3] permanganate,[4] oxide,[5] peroxide[6] and lead tetraacetate[7] have been used in stoichiometric amount for the oxidation reactions. Alternatively, in catalytic transfer hydrogenation strategy,[8] a stoichiometric amount of sacrificial organic acceptor has also been employed to achieve this process and also generates stoichiometric amounts of organic waste. On the contrary, catalytic dehydrogenative oxidation is a more sustainable alternative to the traditional methods, because no stoichiometric oxidant is required and is more atom economical, and the only byproduct is hydrogen, which is valuable itself and can be removed to shift the equilibrium toward the products or can be used to hydrogenate unsaturated intermediates in situ, (see borrowing hydrogen reactions) eventually generated from condensation reactions in one-pot strategies. Therefore, catalytic acceptorless dehydrogenation has become an expedient process for the manufacturing of useful chemicals.



Scheme 1.1: (a) Conventional dehydrogenation reactions, (b) hydrogen-transfer reactions, (c) acceptorless dehydrogenation reaction.

In general, acceptorless dehydrogenation involves the conversion of less reactive substrates such as alcohols, alkanes or amines into more reactive ones, such as carbonyl

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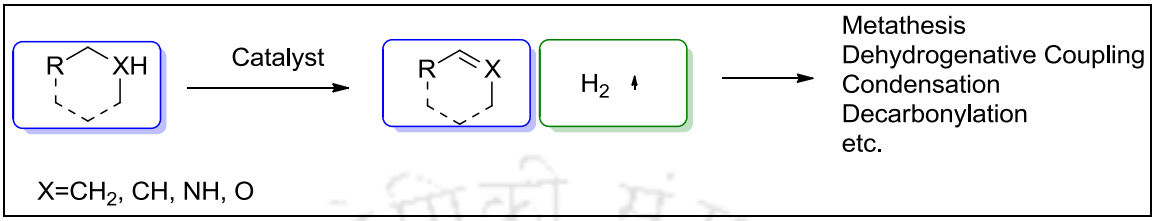
compounds, alkenes or imines. The corresponding highly active insitu formed oxidized products can readily be converted into various valuable products *via* tandem reactions occurring in the same reaction vessel (Scheme **1.2**).



Scheme 1.2: Acceptorless dehydrogenative transformations

1.2.1. Dehydrogenation of alcohols:

86% of our energy requirement and 96% of our organic chemicals were supplied by fossil fuels.[9] However, fossil resources are not renewed and the consumption of fossil resources may result in a harmful effect on the environment. In the future, to fulfill global energy demands, we need to increase our energy demands by 50%.[9] Therefore, much rapid depletion of fossil fuel is expected which urge chemist to find some alternative energy source to fulfill the global energy demand from natural resources. The alcohols are very essential substrates in organic synthesis and can be renewably obtained from lignocellulosic biomass,[10] like agricultural waste, garbage, wood and forestry. By using the dehydrogenation strategy, alcohol can be converted to other valuable products and fine chemicals.[11] Moreover, H_2 evolution has been taking place during the dehydrogenation reaction of alcohol, and one can use this H_2 in hydrogen fuel cells as an alternative energy source. In this perspective alcohol dehydrogenation is an essential area of research in organic synthesis.

Production of chemicals from biomass *via* condensation reactions such as Guerbet reaction, aldol condensation, esterification, ketonization and etherification have been developed by minimizing the loss of carbon molecules.[9] Furthermore, biomass may also be turned into syngas, a complementary and alternate method for converting biomass into chemical building blocks. Nowadays, 90% of ethanol is produced from

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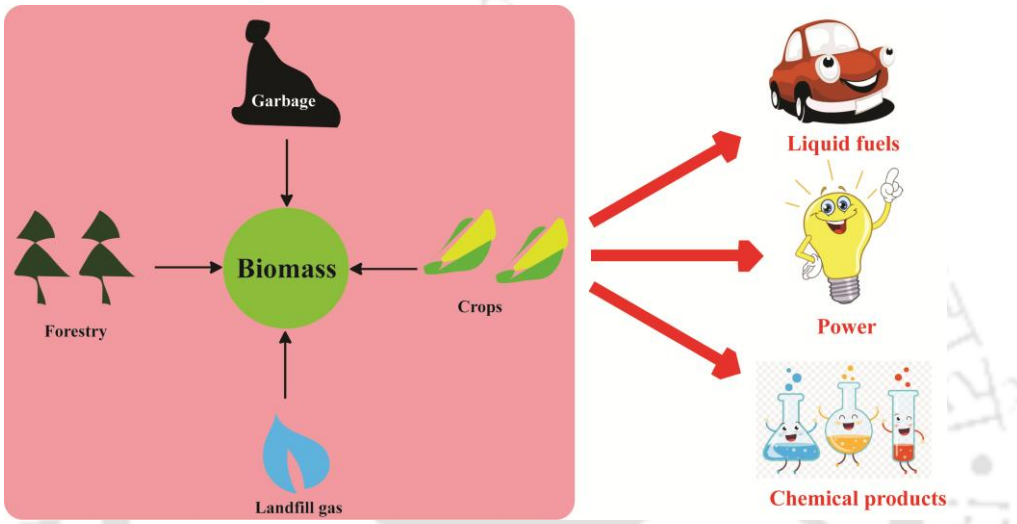
biomass mostly from sugar.[12] Various alcohols like butanol or higher alcohol can produce from biomass *via* Guerbet reaction. Acid, glycerol, acetone, furans, lactic acid and some important heterocyclic compound can be synthesized directly from alcohol by applying different dehydrogenative organic reactions. As a result, biomass may be used as a renewable raw material for power generation, fuel production, and chemical synthesis (Scheme **1.3**).



Scheme 1.3: Uses of biomass to power generation, fuel production, and chemical synthesis

Thus, the applicability of biomass-derived alcohols to synthesize valuable chemicals is highly desirable. However, alcohols typically need to be oxidized to more reactive carbonyl compounds in order to operate in effective C-C or C-Heteroatom bond formation in organic synthesis. The traditional ways to perform the oxidation of alcohols involve the use of strong oxidants in a stoichiometric amount, leading to an equivalent amount of toxic waste. Conventional methods include the use of chromium-based,[13] manganese-based,[14] silver based[15] and DMSO-based reagents.[16] A more modern approach involves the use of TEMPO[17] (2,2,6,6-tetramethyl-1-piperidinyloxy), Dess-Martin Periodinane,[18] *o*-iodoxybenzoic acid (IBX),[19] sodium hypochlorite (NaOCl)[20] and biologically inspired oxidation catalyst[21] etc.

Therefore, converting alcohols to various valuable chemicals *via* a green and sustainable approach is highly demanding. In this regard, acceptorless dehydrogenation of alcohols is considered to be a green, atom-economical conversion of alcohol to

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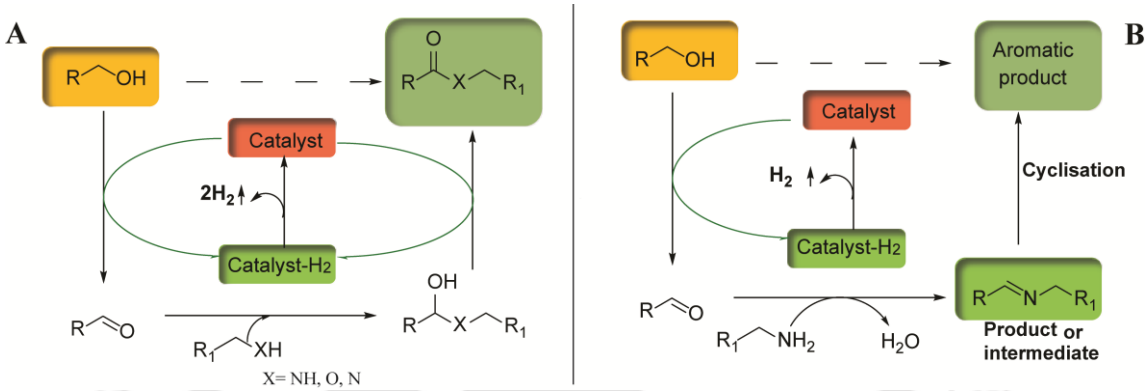
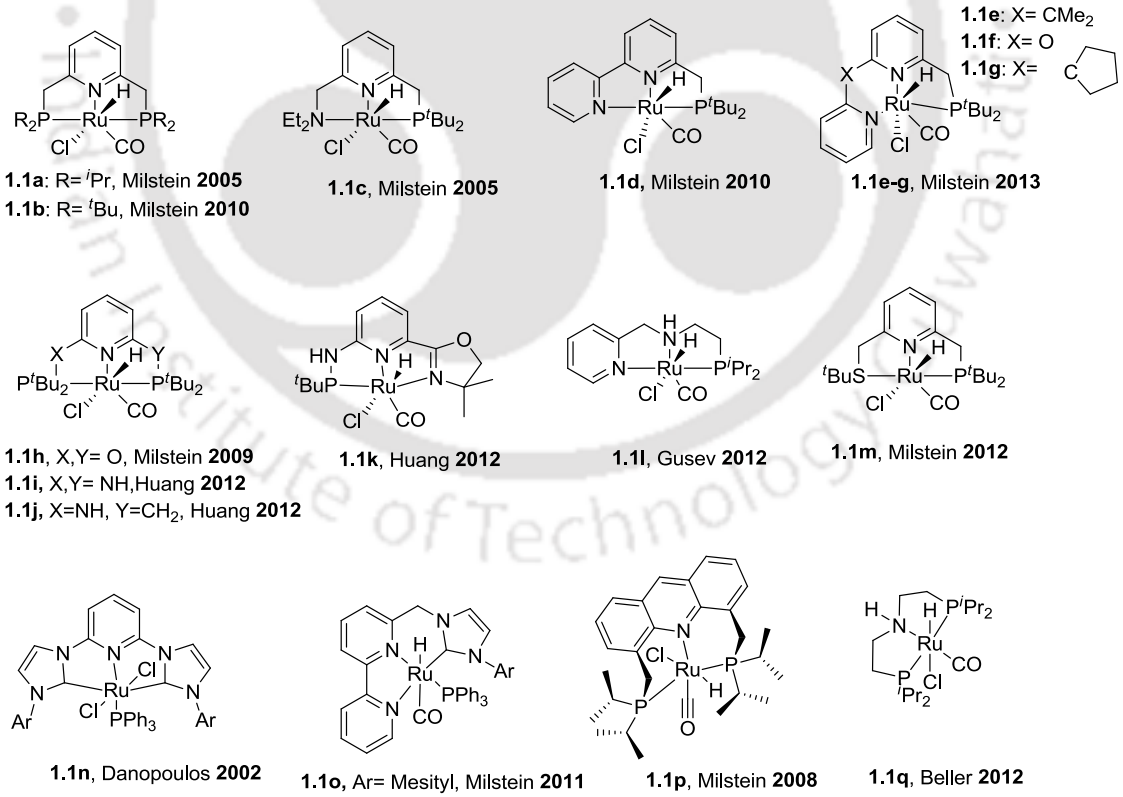
aldehyde and has received significant attention into organic synthesis.[22] Here, transition metal catalyst plays an important role to activate the alcohol molecules to form new reactive aldehyde or ketone by removal of two adjacent hydrogen atoms from alcohol and form transition metal-H_2 complex. After that in-situ formed aldehyde or ketone is



Scheme 1.4: General overview of acceptorless dehydrogenation of alcohol



Scheme 1.5: Ruthenium pincer complexes involve in acceptorless dehydrogenation.

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coupled with different nucleophile resulted in the creation of new carbon-carbon or carbon-heteroatom bond and the hydrogen enriched catalyst-H_2 returns back to its original active catalytic species by elimination of a hydrogen molecule. Here, a brief overview of the AD reaction is discussed (Scheme **1.4**).

Dehydrogenations are endothermic reactions. Thereby, relatively high temperatures required may limit the methodology, due to the instability of many metal complexes at high temperature. Pincer complexes have higher thermal stability and their structural and electronic properties can be finely tuned by rational design, leading to unpreceded reactivity. In this regard, various pincer complexes[2e] have been reported which showed excellent catalytic activity toward the dehydrogenation reaction of alcohol (Scheme **1.5**).

1.2.2. Dehydrogenation of alcohols to form aldehydes or ketones:

At pioneering work the acceptorless dehydrogenation of primary and secondary alcohol was proceed through the oxidative addition, which will lead to the development of metal-hydride complex. Next, the *β*-hydride elimination forms the carbonyl compound together with metal dihydride species which upon reductive elimination generating H_2 with simultaneous restoration of the active catalyst. First, *Dobson and Robinson*[23] demonstrated $[Ru(OCOCF_3)_2(CO)(PPh_3)_2]$ **1.2a** catalyzed dehydrogenation of primary and secondary alcohol where the *β*-hydride elimination will lead to the formation of hydride complex $[RuH(OCOCF_3)(CO)(PPh_3)_2]$ **1.2b** and the corresponding aldehyde or ketone (Scheme **1.6**). Subsequently, various different ligand derived metal Ru,[24] Rh[25] or Ir[26] metal complexes, which have been discovered to be active for this process. In most of cases, excessive catalyst loading or an excess of acid in the reaction medium, reduced the method's effectiveness.

Later, *Milstein*[27] developed a very efficient method to describe acceptorless dehydrogenation of primary/secondary alcohol to aldehyde/ketone using an electron-rich, bulky PNP pincer complex **1.2c**. Next, *Baratta and co-workers*[28] reported the ruthenium *CNN* pincer complexes **1.2d** and **1.2e** containing an NH donor, also known as osmium complexes. When heated to 130 °C

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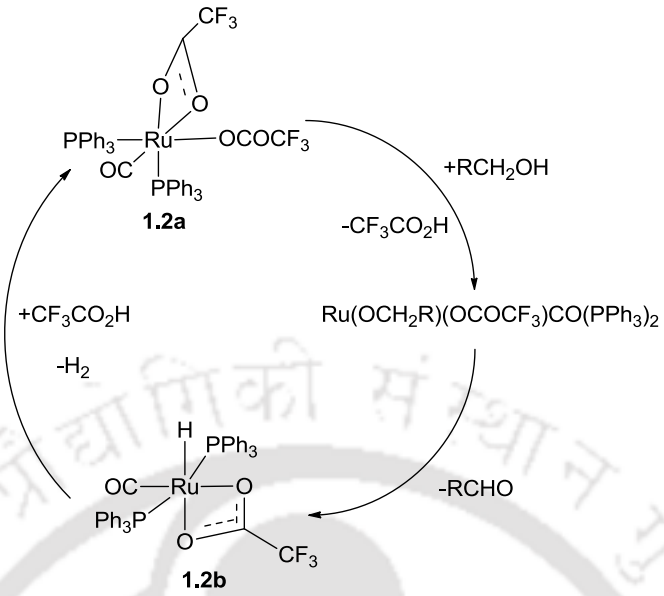
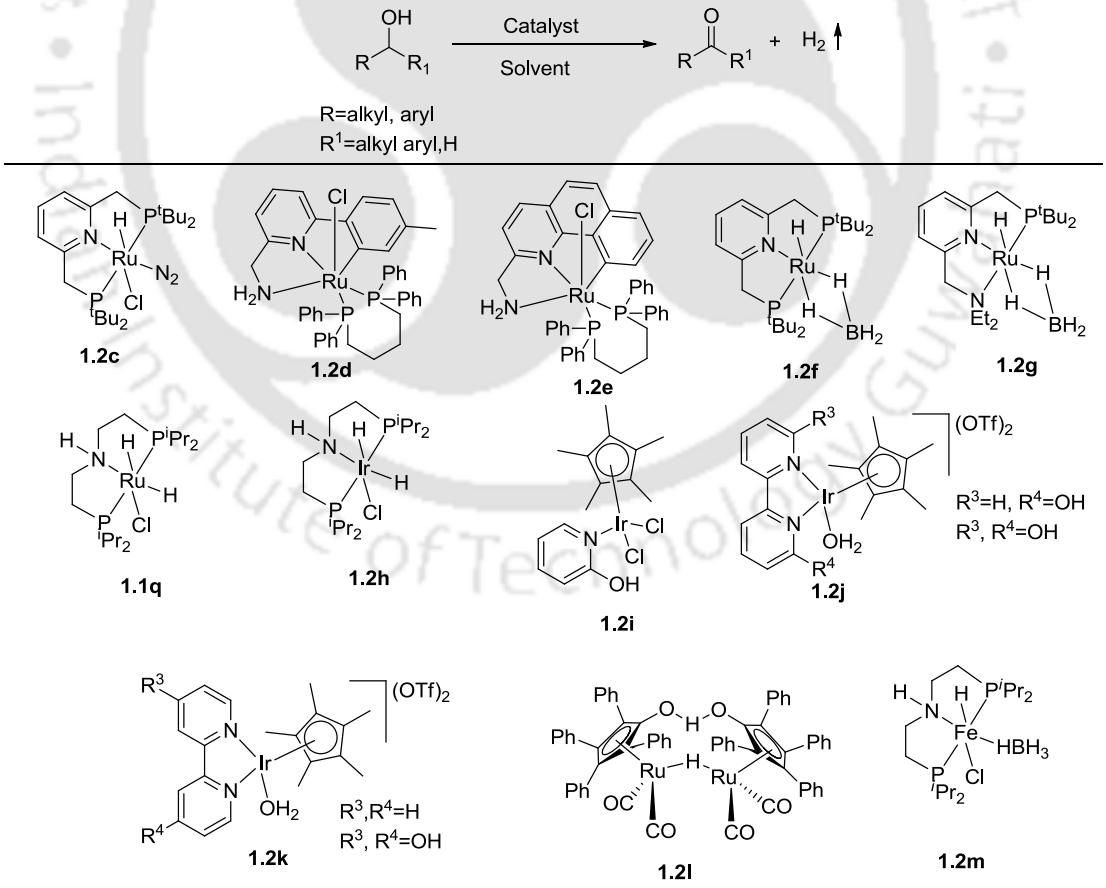


Scheme 1.6: Acceptorless dehydrogenation *via* β-hydride elimination pathway



Scheme 1.7: Dehydrogenation of alcohols to form aldehyde or ketone

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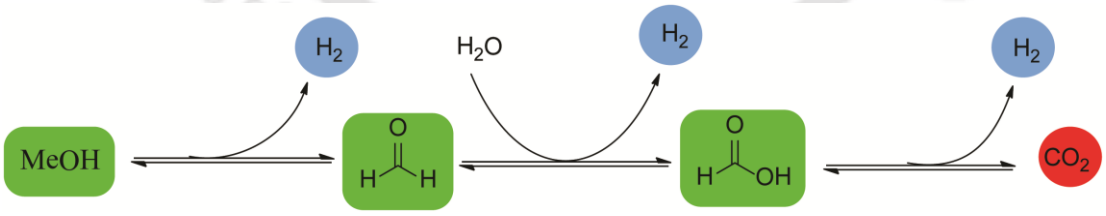
in tert-butanol, osmium complexes accelerated the dehydrogenation of 2° alcohols in the presence of base. After that, the electron-rich *PNP* and *PNN*-ruthenium(II)hydridoborohydride pincer complexes **1.2f** and **1.2g** were developed by Milstein group to dehydrogenate secondary alcohol in neutral condition and catalyst **1.2f** was superior than the catalyst **1.2g** towards this reaction.[29] *Beller and co-worker*[30] have reported a number of known Ru and Ir (**1.1q**, **1.2d**, **1.1c**, **1.2h**) complexes and apply those for the acceptorless dehydrogenation of secondary alcohols, with remarkable TONs and TOFs. In the year 2007, *Yamaguchi and co-workers*[31] applied the iridium complex **1.2i** to catalyse the dehydrogenation of secondary alcohols. Benzyl alcohol gave only 24% benzaldehyde even with 1 mol% catalyst loading. After that by changing ligand scaffold (complex **1.2j-k**), they are able to dehydrogenation of both primary and secondary alcohols, to obtain the corresponding aldehydes or ketones in good yield. Next, *Hong*[32] reported alcohol dehydrogenation with Shvo's catalysts and $RuH_2(CO)(PPh_3)_3$ (**1.2l**) in a neutral reaction medium. In recent time, dehyrogenation of secondary alcohols to ketones with earth-abundant transition metal complex **1.2m** was reported by *various group*[33] (Scheme **1.7**).

1.2.3. Dehydrogenation of Methanol:



Scheme 1.8: Schematic representation of MeOH dehydrogenation

Due to depletion of fossil fuel and growing concern about environmental awareness, people are searching for alternative raw materials. In this perspective, the dehydrogenation of methanol derived from biomass gains much more attention.[22] But dehydrogenation of methanol is a challenging task as large enthalpy (ΔH for methanol is

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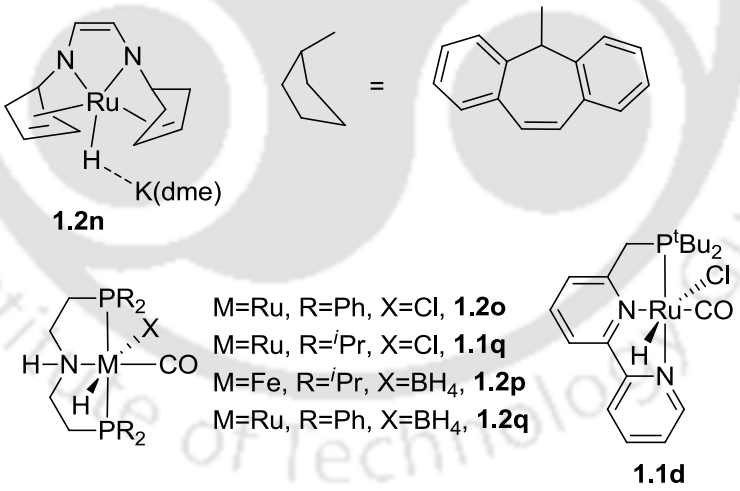
+84 kJ mol^{-1})[34] is required to convert methanol to formaldehyde with harsh reaction conditions. Homogeneously catalyzed aqueous MeOH dehydrogenation to form H_2 and CO_2 is a stepwise transformation, where a few organic intermediates must exist (Scheme **1.8**).[35]

Thermal dehydrogenation of alcohol to produce H_2 in the presence of water was first published by *Cole-Hamilton*[36] with $[Rh(bipy)_2]Cl$ as homogeneous catalyst. When compared to methanol, other alcohols like butane-2,3-diol, isopropanol and ethanol produced about 100 times more hydrogen. After almost 25 years, Grützmacher[37] and Beller,[38] simultaneously reported homogenous ruthenium complex (**1.2n**, **1.2o** and **1.1q**) catalyzed dehydrogenation of MeOH to hydrogen (H_2) and carbondioxide (CO_2) under basic condition, with nearly non-existent CO contamination (Scheme **1.9**). To remove base from reaction medium, *Beller* recently reported a bicatalytic system including ruthenium pincer complexes **1.2p** and **1.2q**[39] for the production of hydrogen and carbon dioxide gases. Very recently, Milstein described ruthenium catalyst **1.1d** is able to promote the same transformation.[40]



Scheme 1.9: Homogeneous catalysts involve in the aqueous dehydrogenation of MeOH to H_2 and CO_2

1.2.4: Dehydrogenative coupling of alcohols to form esters:

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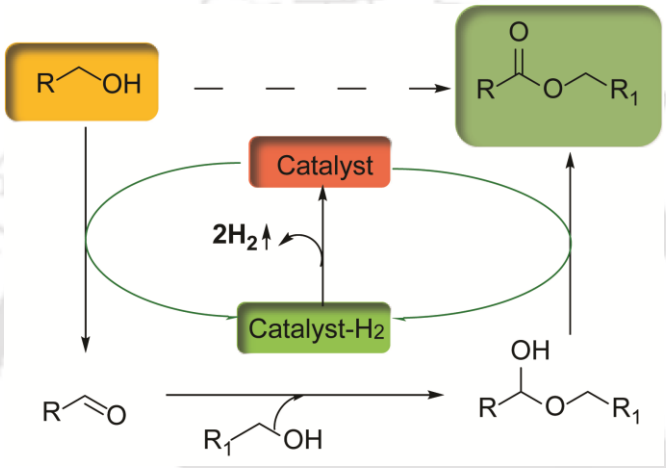
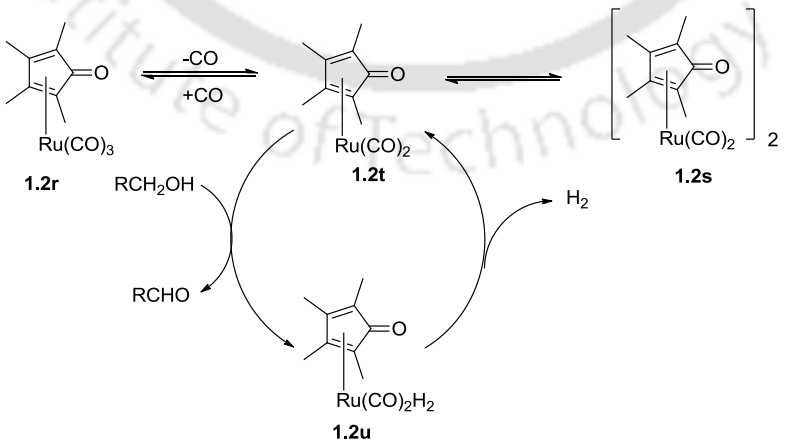
Esterification is one of the most significant reactions in synthetic organic chemistry, having applications in precision chemical manufacturing ranging from fragrances to pharmaceuticals. Typically, the process of esterification is the reaction of an organic acid (RCOOH) with an alcohol (ROH) to produce an ester (RCOOR) and water. For, last two decades, alternative green strategies for the production of esters were established *via* the dehydrogenative coupling of alcohols (Scheme **1.10**).[41-49]



Scheme 1.10: Dehydrogenative coupling of alcohol to form ester

In 1985, *Shvo and co-worker* reported (η^4-tetracyclone)$(CO)_3Ru$ **1.2r** and $[(\eta^4$-tetracyclone)$(CO)_2Ru]_2$ **1.2s** catalyzed acceptorless direct oxidation of primary alcohol to ester. Both the catalysts are involved in this transformation and the true catalytic species is the coordinatively unsaturated complex **1.2t** (Scheme **1.11**).[41]



Scheme 1.11: Dehydrogenative coupling of alcohol to form ester presented by Shvo.

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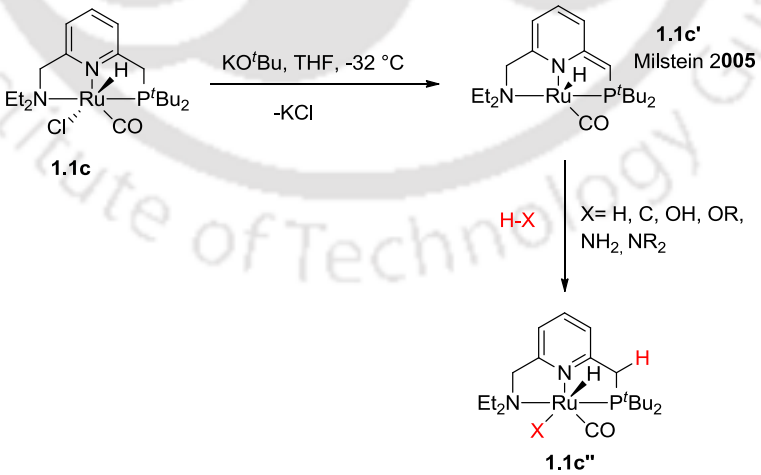
After 2 years, in 1987, *Murahashi and co-workers*[42] demonstrated $RuH_2(PPh_3)_3$ catalysed, effective transformation of alcohols to esters and lactam at very high temperature 180 °C. *Milstein*[43] then demonstrated a metal-ligand co-operation (MLC) (Scheme **1.12**) which resulted in high-efficiency towards the conversion of alcohols to esters (Scheme **1.13**). The mechanism of the reaction is depicted in Scheme **1.14**. The acridine complex, **1.1p** prepared by *Milstein* group[44] also catalyzed this reaction with a catalytic amount of base under neat conditions or in refluxing solvent. The catalytic conversion of bio-renewable ethanol to ethyl acetate was very efficient with Ru-MACHO **1.2p** and PN^{H}N pincer complex **1.2v** was reported by *Gusev and his group.*[45] However, it was also designed to synthesize unsymmetrical esters, from the coupling of two distinct alcohols (primary and secondary alcohols)[46] (Scheme **1.15**). A new method of transesterification[47] reaction is the acylation of secondary alcohols using esters and H_2 will liberate. Previously, lactonization of 1,4- butanediol to γ-butyrolactone was reported with ruthenium-catalyst at 205 °C.[48] Later, ruthenium hydrido borohydride complex **1.2h** catalyzed lactonizations of primary-primary diol, as well as primary-secondary diol have been reported.[29] *Robertson and co-workers* demonstrated the synthesis of polyesters, by applying the dehydrogenative coupling strategy of alcohols.[49a] Some earth abundant metal also developed to effective transformation of alcohols to esters.[49b-f]



Scheme 1.12: MLC based on deprotonation/dearomatization-aromatization

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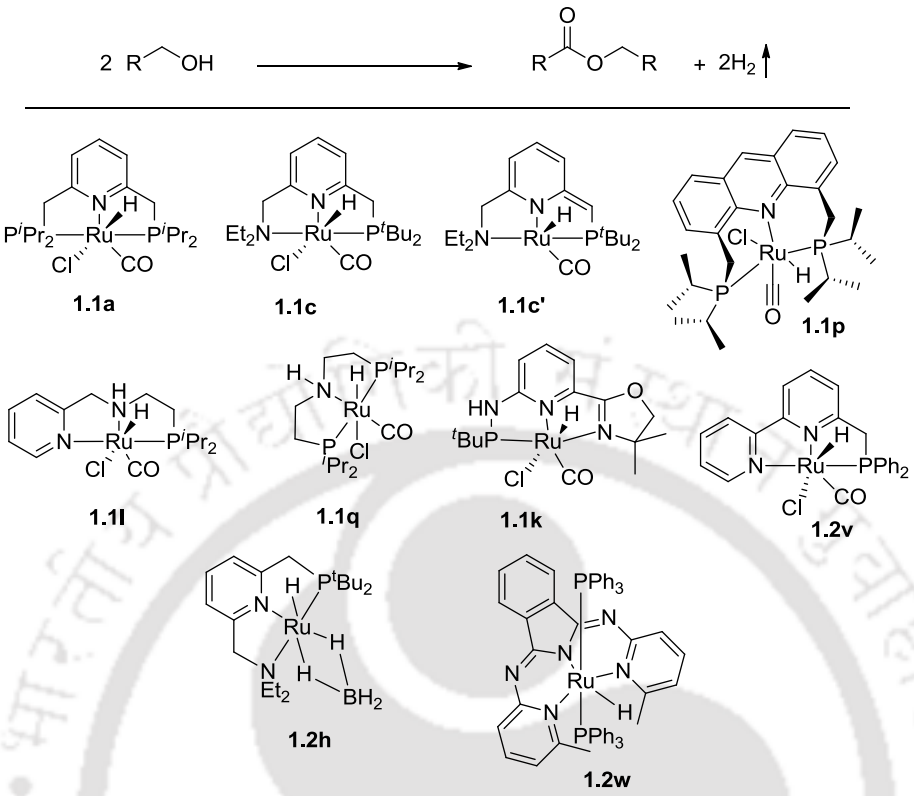
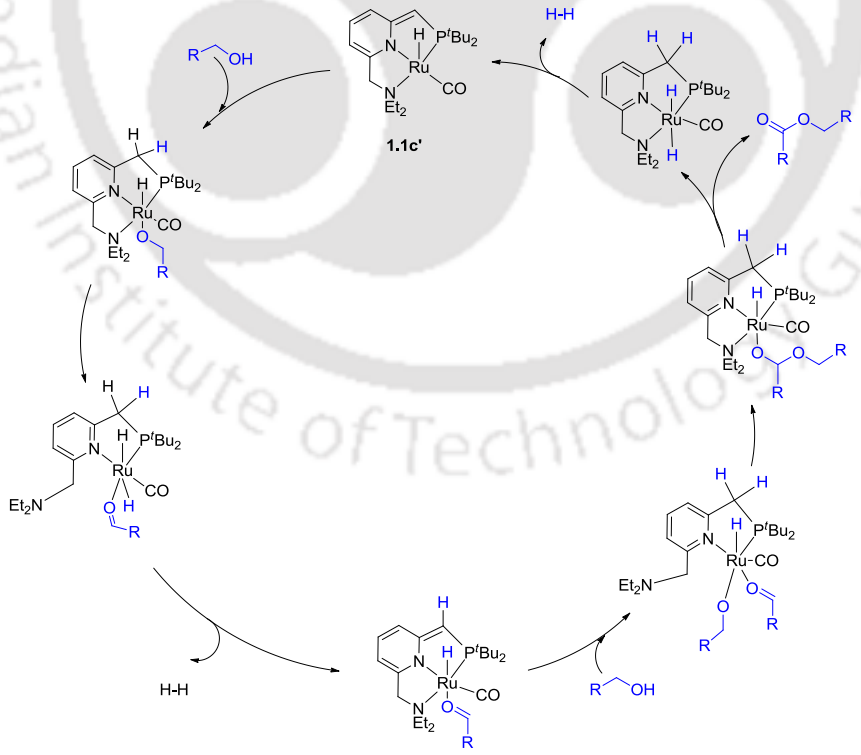


Scheme 1.13: The dehydrogenative synthesis of ester by ruthenium complexes.



Scheme 1.14: Mechanistic cycle for dehydrogenative coupling of alcohols to produce esters with **1.1c '**

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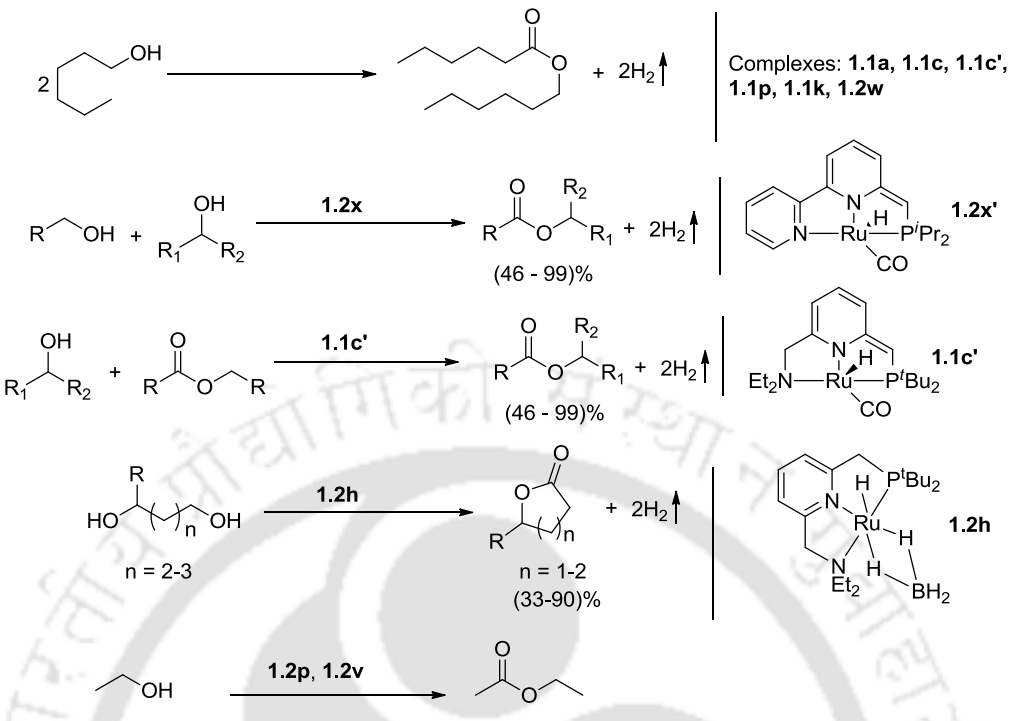

Scheme 1.15: The dehydrogenative coupling of alcohol to form ester.

1.2.5. Dehydrogenative coupling of alcohols to form acetals:

In the dehydrogenative coupling reactions, the intermediate aldehyde might react with two equiv of alcohols to produce an acetal, or it could react with another alcohol to form a hemiacetal, which may then be dehydrogenated further to produce an ester (Scheme **1.16**). At pioneering, *Murahashi and co*-workers[50] reported $[RuCl_2(PPh_3)_3]$ catalyzed acetal formation with 8 TON. Next, the TON increased to 30 by using a rhenium complex,[51] is also reported. A very efficient acetal formation was reported by *Milstein group*[44] in 2009, where acridine-PNP ruthenium pincer complex (0.1 mol %) was used and a unique "long-range" MLC was observed (Scheme **1.17**). The reaction of catalyst **1.1p**, with H_2/KOH results dearomatized ruthenium complex **1.1r** on the core acridine ring because of the heterolytic activation of H_2 (Scheme **1.17**). Single-crystal X-ray diffraction and spectroscopic data of the complex confirmed the dearomatization of the core acridine ring. Similarly, complex **1.1p** was reacted with D_2/KOH to produce complex **1.1s**, which had heterolytic activation of D_2. In 2012, same group reported

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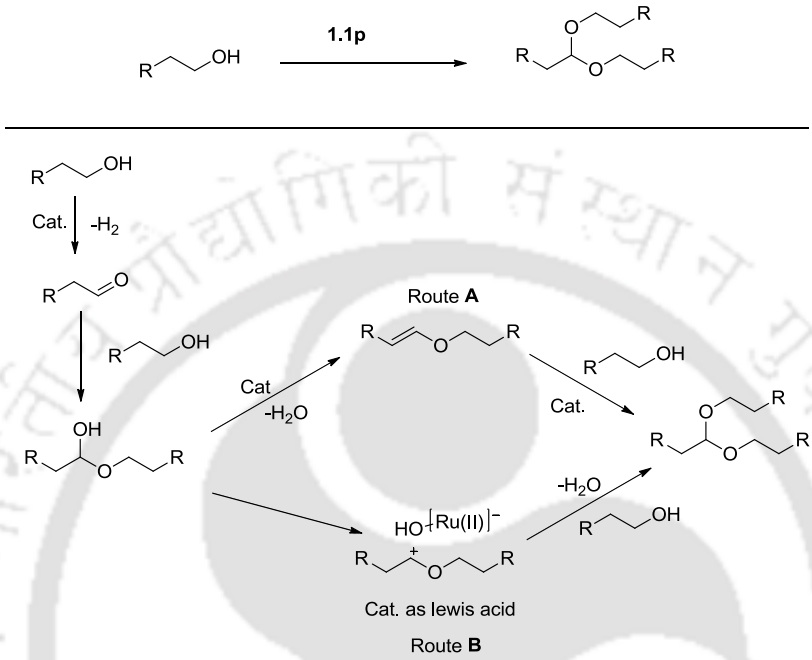
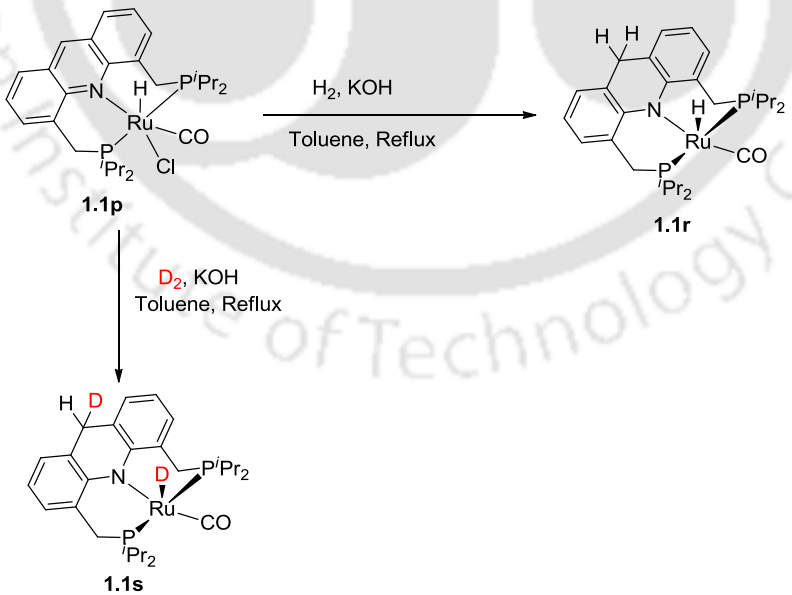
ruthenium sulphate complex $[Ru(\eta^2\text{-}SO_4)(PPh_3)_2(CH_3CN)_2]$ catalyzed acetal formation, efficiently at low temperature condition and the mechanism goes *via* an acid-catalyzed pathway.[52]



Scheme 1.16: Proposed pathways for acetalization



Scheme 1.17: Acridine-PNP ruthenium pincer complexes (**1.1p**) with long-range MLC

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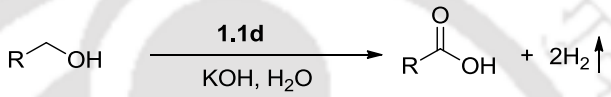
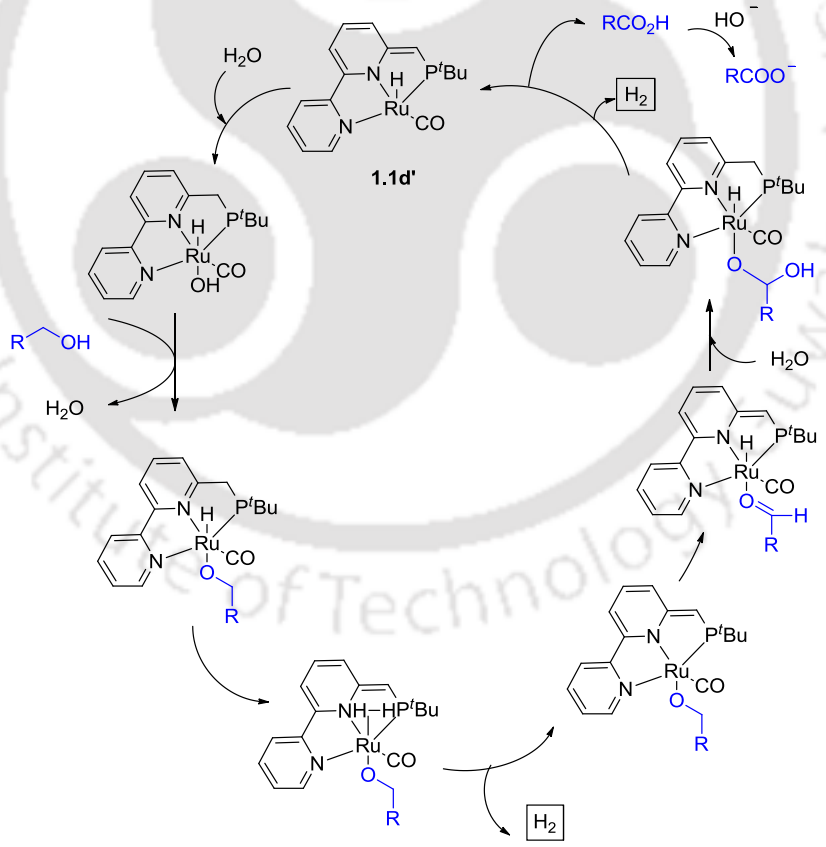
1.2.6. Dehydrogenative synthesis of acids from alcohols:

The most significant approach in organic synthesis is the direct conversion of alcohols in presence of water to form carboxylate salts by removal of H_2, which reduces the need for stoichiometric oxidants and chlorinated solvents.[53] Here, water serves as both an oxygen donor and a reaction medium. *Milstein*[54] reported this transformation with complex **1.1d**, with very good yield, exhibiting excellent atom economy. The proposed mechanistic cycle of this conversation has been depicted in scheme **1.19**. After publication of this work, in the same year *Grützmacher*[37] also reported the conversion of alcohols to carboxylic acids with Ru-catalyst.



Scheme 1.18: The dehydrogenative synthesis of acid from alcohol.



Scheme 1.19: Proposed catalytic cycle converting alcohols to carboxylates

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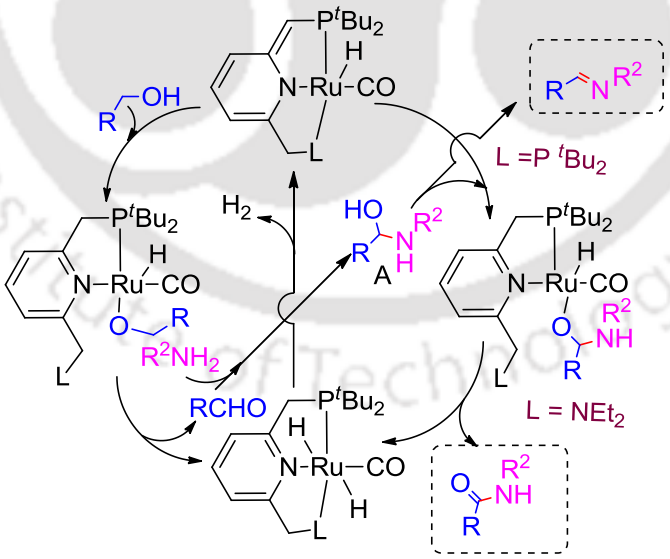
1.2.7. Dehydrogenative coupling of alcohols and amines to form imine and amides:

Dehydrogenative coupling of alcohols and amines may result in the formations of either amides or imimes. The selectivity lies onto the nature of catalyst or the ligand scaffold. Double dehydrogenation results in amide formation and dehydrogenation followed by dehydration furnished an imine formation (Scheme **1.20**). *Milstein*[55] proposed *PNN* ruthenium complex catalyzed selective synthesis of amide directly from alcohol and amine with the liberation of H_2. They proposed the mechanism of this reaction where the hemilability of the NEt_2 ligand is responsible to further dehydrogenate the hemiaminal intermediate **A**, which leads to the amide formation (Scheme **1.20**). After that, diverse catalytic systems with homogeneous[56] and heterogeneous[57] catalysts were reported for the synthesis of amides from alcohols and amines. *Dong and Guan's groups* also reported amide synthesis with Ru-MACHO catalyst.[58] The strategy is further extended by the *Milstein group* to achieve the synthesis of polyamides and peptides directly from diols and diamines.[59] The same group also reported the dehydrogenative synthesis of amide by the reaction of ester and amine[60] (Scheme **1.21**).



Scheme 1.20: Proposed catalytic cycle for the synthesis of amides and imines from alcohols and amines

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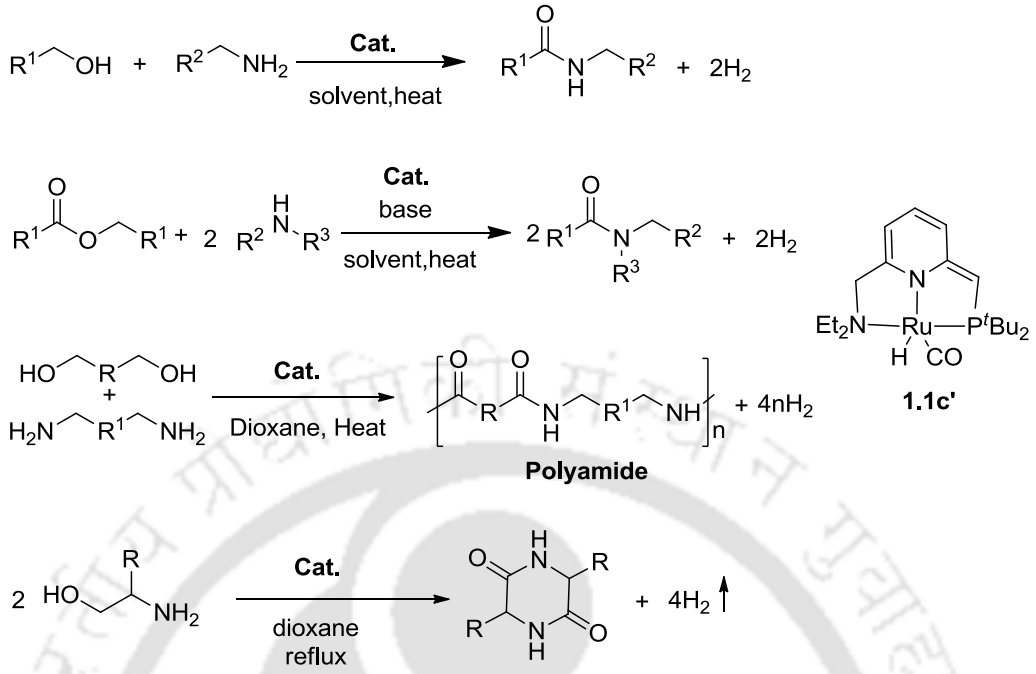
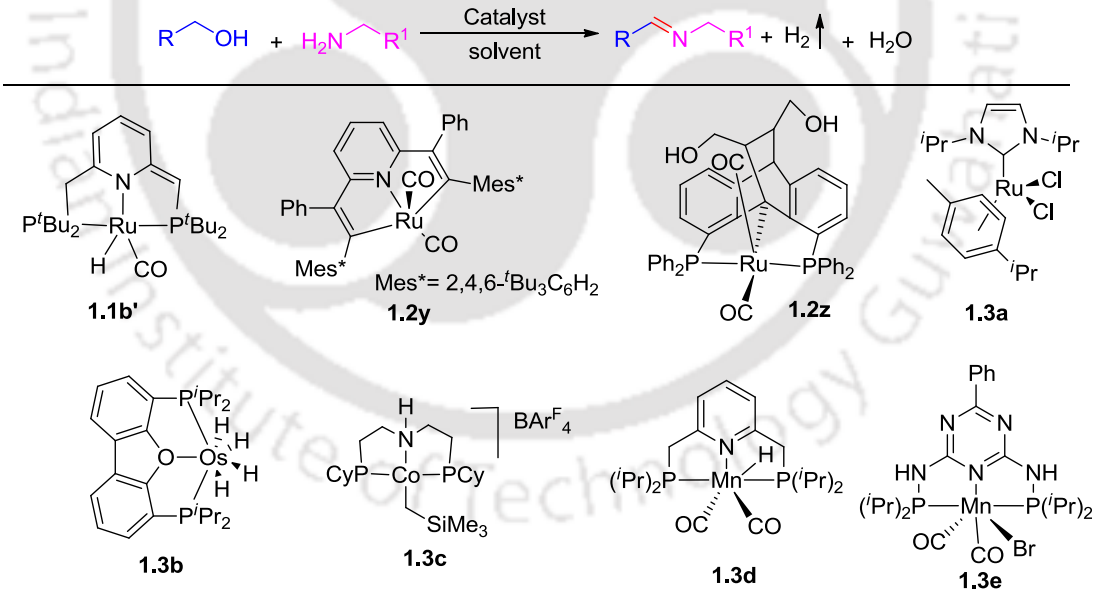


Scheme 1.21: Dehydrogenative coupling of alcohols to amide



Scheme 1.22: Alcohols to imine *via* dehydrogenative coupling

The PNP complexes **1.1b′** developed by *Milstein group*[61] afforded the development of imines from alcohols and amines. After that, several imine formations have been reported with diverse catalysts.[62] This imine formation from alcohols and

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amines was also accelerated by the PNP Ru-pincer complex **1.2y**[63] and a PCP Ru-pincer complex **1.2z**,[64] both of which work *via* MLC. This transformation was later reported, catalysed by a Ru-carbene complex **1.3a**[65] and an OsPOP[66] [POP: 4,6-bis(diisopropylphosphino)dibenzofuran] complex **1.3b**. Very recently, Co-complex[67] and Mn-complexes[68] were shown catalytic activity towards the dehydrogenative coupling (Scheme **1.22**).

1.2.8. Dehydrogenative coupling of alcohols to form C=C:

1.2.8a. *Aldol condensation:*

The aldol condensation process is a well-known method for forming C=C bonds in organic synthesis. It is an aldehyde or ketone condensation process that produces unsaturated molecules in the presence of acid or base.[69] The aldol condensation process may be used to generate more complex ketone or alcohol molecules from renewable alcohols by employing the acceptorless dehydrogenation principle. In 2006, *R. Martínez et al.*[70] reported coupling of bicyclic ketone derivatives with alcohols under ambient conditions to synthesize *α,β*-unsaturated ketone derivative with $RuCl_2(DMSO)_4$. Later, several transition metal catalysts Pd,[71] Pt,[72] Au,[73] Ti[74] were developed for the production of *α,β*-unsaturated ketones using alcohols. Very recently, *Gunanathan*[75] *and Banerjee*[76] developed manganese (**1.3.e'**) and $Fe(OAc)_2$ catalyzed, *α*-alkenylation of ketones using primary alcohols. Again, *α,β*-unsaturated compound have been reported with primary and secondary alcohol with various homogeneous[77] and heterogeneous[78] catalyst *via* aldol condensation reaction (Scheme **1.23**). Moreover, *α*-alkenylation of sulfones,[79] *N*-heteroarenes[80] and amides[81] have also been reported to construct C=C bond *via* aldol type condensation reaction.

1.2.8b. *Wittig Reaction:*

Milstein and co-workers[82] have shown the selective synthesis of alkene directly from alcohol through catalytic oxidant-free Wittig reaction in presence of phosphine

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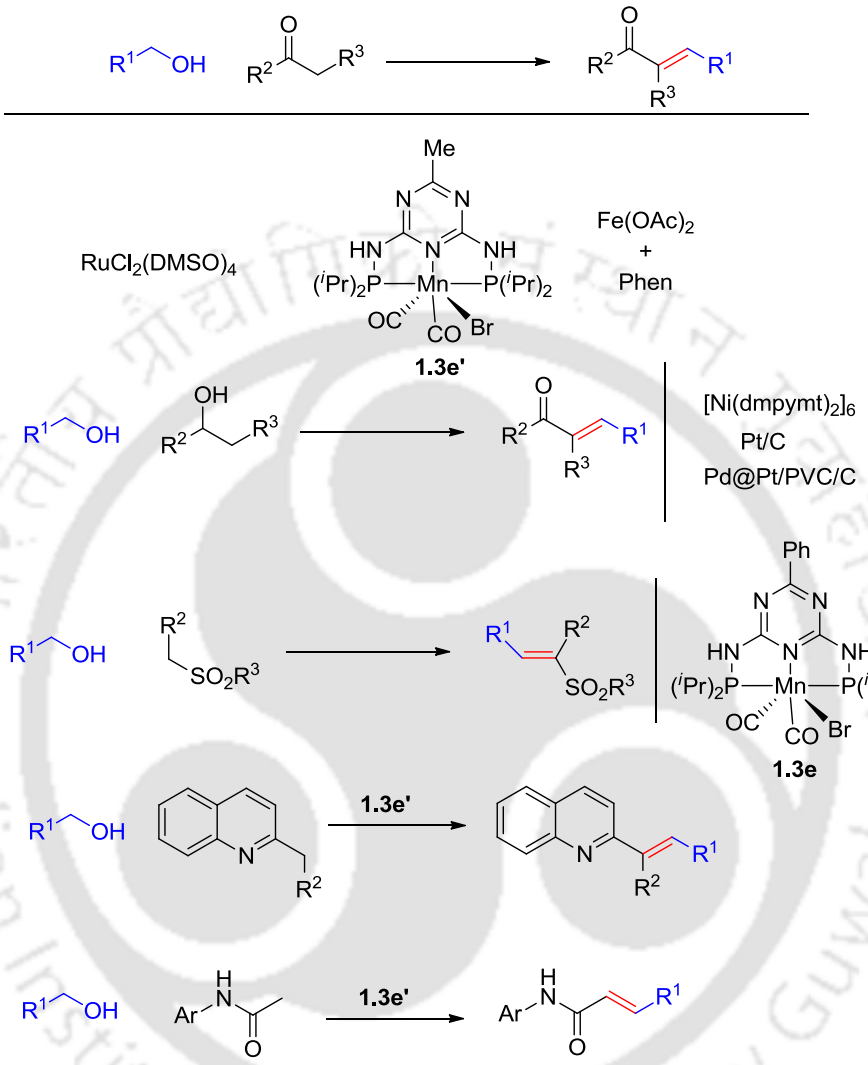
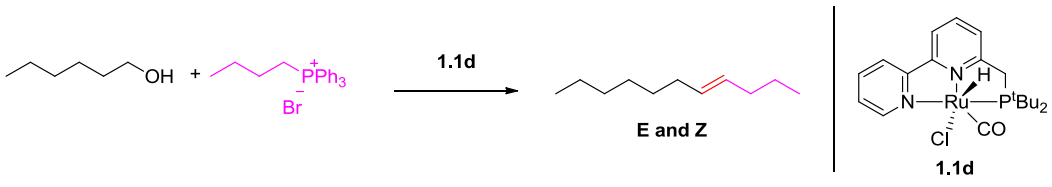
based-ruthenium pincer complex (Scheme **1.24**). The reaction uses low catalyst loadings and the reaction leads to Z (aliphatic) or E (benzylic) stereospecificity.



Scheme 1.23: C=C bond foration *via* aldol reaction



Scheme 1.24: C=C bond foration *via* Wittig reaction

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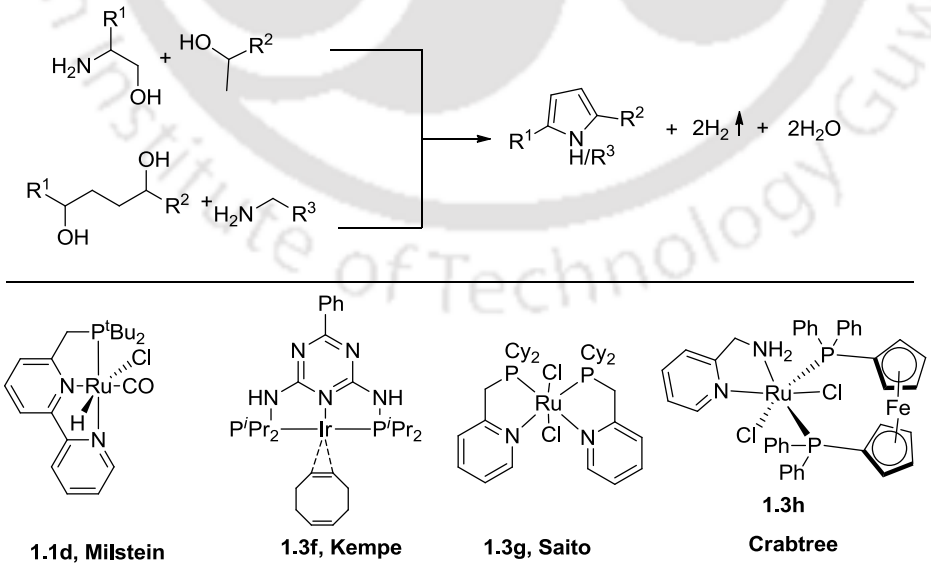
1.2.9. Dehydrogenative coupling of alcohols to form heterocyclic compounds:

The discovery of novel, simple, and atom-economical methods to synthesise heteroaromatics such as pyridines, quinolines, pyrroles, and pyrazines from cheap starting materials would be particularly appealing owing to the wide variety of applications[83] of these compounds. Construction of these heteroaromatic compounds was reported with diverse ruthenium pincer complexes with excellent reactivity directly from amino alcohols.

1.2.9a. *Synthesis of pyrroles from secondary alcohols with β-amino alcohols:*

In 2013, *Kempe*[84] reported iridium **1.3f** catalyzed pyrrole formation from secondary alcohols and *β*-amino alcohols *via* acceptorless dehydrogenation under very mild reaction conditions. During the process, two equivalents of hydrogen gas are eliminated. After that, in the same year, *Milstein* group[85] performed this efficient transformation with the bipyridine derived Ru-PNN complex **1.1d** with excellent yield. This reaction was also extremely efficiently performed by a "PN" ligated bidentate ruthenium complex **1.3g** developed by *Saito and coworkers*.[86] *Beller*[87] *and Crabtree*[88] also synthesized *N*-alkylated pyrrole from dehydrogenation of diol and amine (Scheme **1.25**).



Scheme 1.25: Synthesis of pyrroles from secondary alcohols and *β*-amino alcohols

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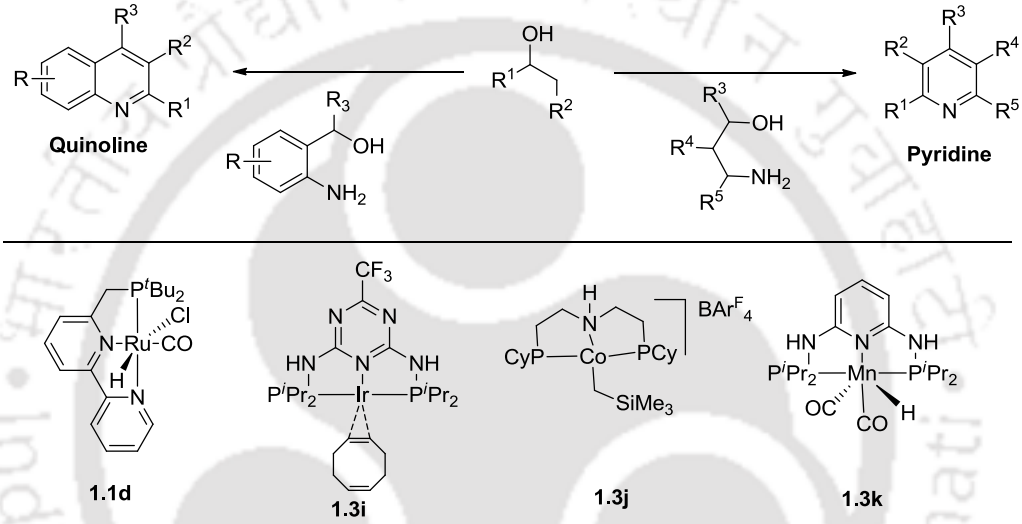
1.2.9b. *Pyridines and quinolines from γ-amino alcohols.*

The synthesis of pyridine and quinoline can be achieved if *γ*-amino alcohol is used in place of *β*-amino alcohol. As expected, the reaction of secondary alcohol with *γ*-amino alcohols gives pyridines and quinolines with complex **1.1d**.[89] In the same year, *Kempe*[90] also reported iridium catalyzed **1.3i** synthesis of pyridine with primary alcohols and *γ*-amino alcohols. Some earth-abundant transition metals[91] are also reported towards this heterocyclic synthesis (Scheme **1.26**).



Scheme 1.26: Synthesis of quinolines and pyridines

1.2.9c. *Pyrazines from β-amino alcohols.*

Homocoupling of *β*-amino alcohols may lead to the formation of pyrazine derivatives. Dearomatized *PNP* Ru-pincer complex **1.1b**',[59c] leads to the formation of pyrazine with moderate yield. Next, *Balaraman*[92] *and group* reported cobalt-catalyzed **1.3l** pyrazine synthesis along with pyrrole and pyridine. Very recently *Milstein and co-worker*[93] developed synthesis of pyrazines and quinoxalines derivatives with manganese pincer complexes **1.3m** (Scheme **1.27**).

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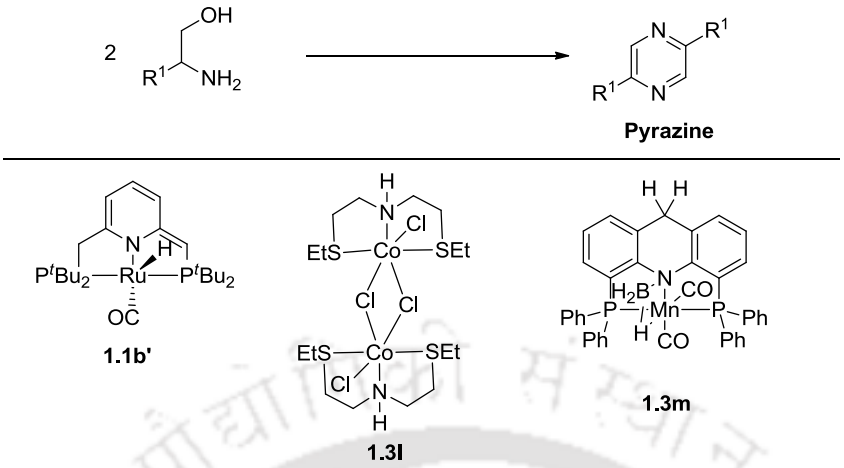

Scheme 1.27: Synthesis of pyrazines from *β*-amino alcohols

1.3. Borrowing hydrogen catalysis:

The Borrowing hydrogen (BH) catalysis[94] is also termed as hydrogen auto-transfer reaction is an important strategy in organic synthesis. In this reaction, catalyst borrow hydrogen from donor molecule making metal hydride species and transfer the hydrogen to the intermediate forming a hydrogenated product. Borrowing hydrogen catalysis really depends on the stability of the metal hydrides which may form during the process of H_2 activation. If the metal hydride is excessively stable, it quickly releases the activated hydrogen, rendering the BH technique ineffective. There are three steps involve in BH strategy a) dehydrogenation with metal catalyst, b) condensation or transformation reaction and c) hydrogenation reaction. The basic scheme of this concept is illustrated bellow (Scheme **1.28**).

In the first step, less reactive molecule (alcohol, amine and alkane) is converted into more reactive substances (aldehyde, imine or alkene) by removing of adjacent hydrogen molecule with the help of metal catalyst. After that in second step, general organic reaction happens (e,g condensation or alkene metathesis or transformation) and it produces active unsaturated compound. In last step, the active unsaturated compound hydrogenated with the help of metal hydride complex. The last step (hydrogenation) is usually thermodynamically favoured reaction and hence it shifted the reaction towards

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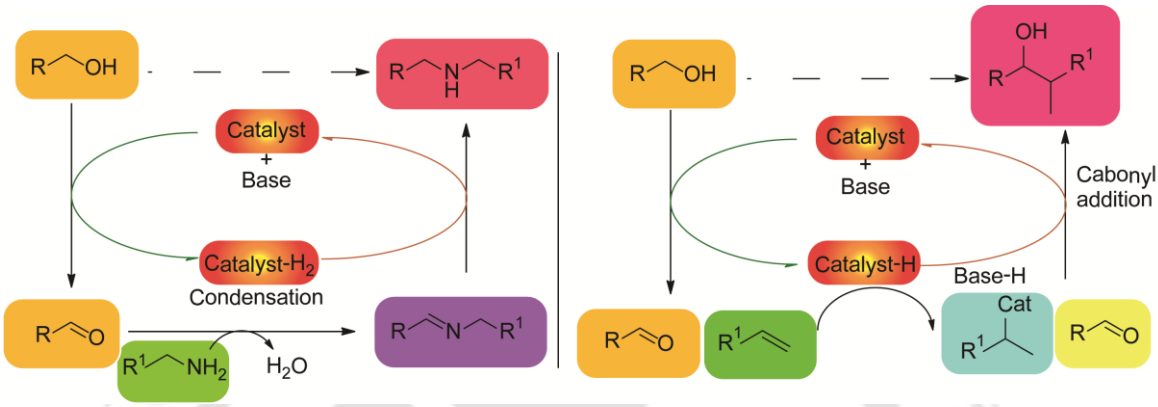
completion. Moreover, it drives the dehydrogenation step to form more reactive intermediate from less reactive donor molecule. It is worth mentioning that BH reaction can considered as a multistep process. Therefore, BH reaction received much more attention in organic synthesis over past few decades.



Scheme 1.28: Basic scheme of the borrowing hydrogen methodology (BH).

1.3.1. Activation of alcohols:

The activation of alcohol to aldehyde usually carried out by dehydrogenation reaction. In borrowing hydrogen process a temporary transformation of alcohol into aldehyde happened and transform to an unsaturated product followed by subsequent hydrogenation to form C-C or C-N bond.

1.3.1.1. C-C bond formation.

1.3.1.1a. Aldol condensation:

The C-C bond formation *via* aldol condensation reaction is a well known approach in organic synthesis. It is a condensation reaction of aldehyde or ketone in presence of acid or base and afforded *α,β*-unsaturated compounds.[95] Using borrowing hydrogen principle, one could be able to perform aldol condensation reaction to synthesize more complex ketone or alcohol molecule from renewably obtained alcohols. In BH reaction strategy first dehydrogenation of alcohol takes places to form aldehyde or ketone, after that condensation reaction happened and lastly hydrogenation reaction taking place to form corresponding ketone or alcohol (Scheme **1.29**).

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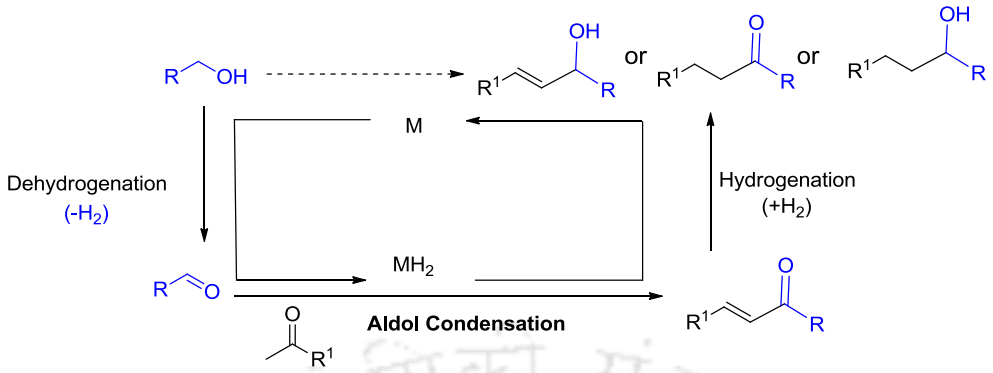
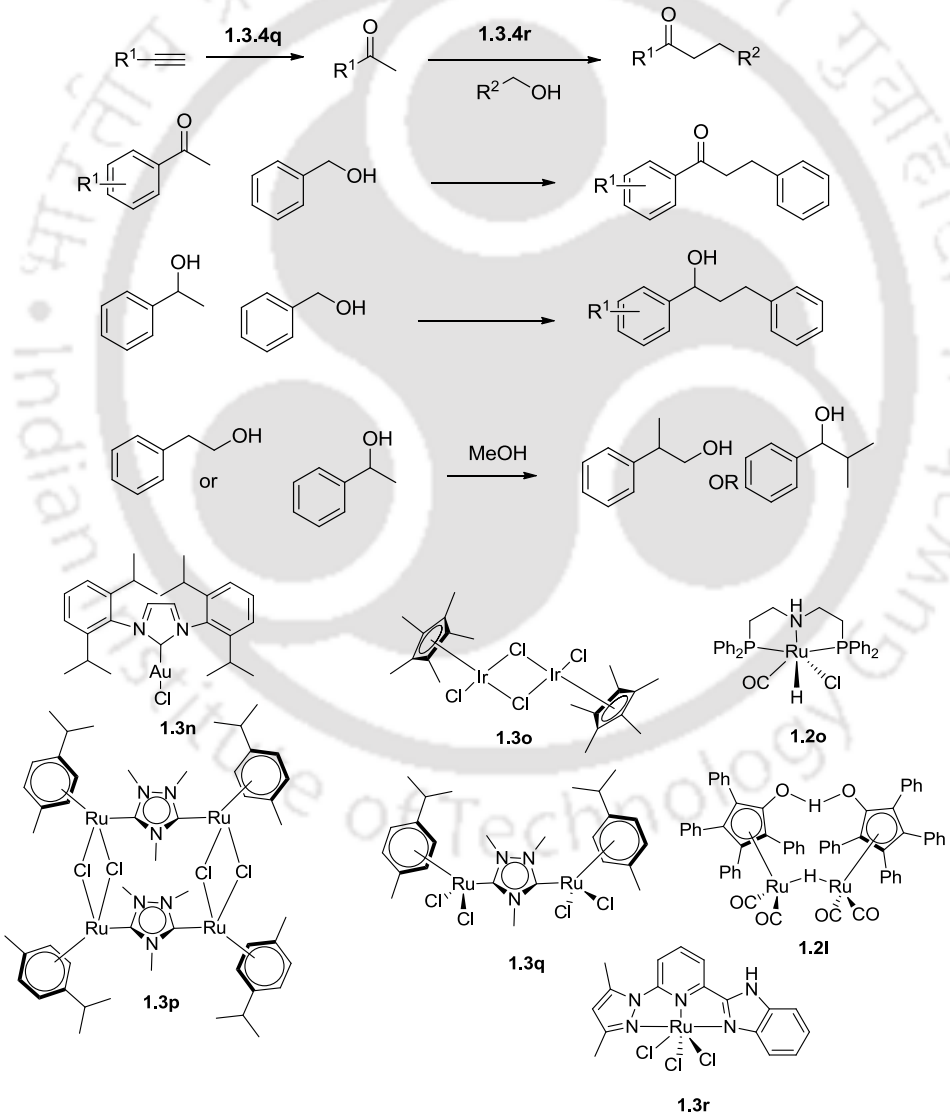


Scheme 1.29: An aldol condensation is depicted schematically in the BH technique.



Scheme 1.30: C-C bond formation reactions

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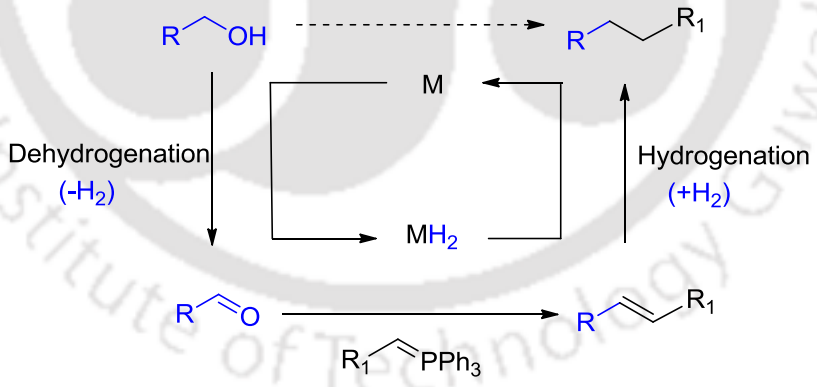
Iridium[96] and ruthenium-based[97] complexes have been widely applied for the *α*-alkylation of ketones with primary alcohols and give excellent selectivity towards product formation. A different strategy involved where *α*-alkylation of ketones happened together with the hydration reaction of alkynes with **1.3n** complex[98] (Scheme **1.30**). Another, BH reaction have been reported involving primary and secondary alcohol and afforded *β*-alkylated products[99] (Scheme **1.30**). Methylation of ketone[100] and alcohol[101] also reported with various catalysts using methanol as methylated agent. Moreover, *α*-alkylation of amide[102], ester[103] or nitrile[104] has been developed. Recently, earth-abundant transition metal (Mn, Ni, Fe)[105] complex catalyzed alkylation reactions have been reported.

1.3.1.1b. *Wittig reaction:*

It is a very well known procedure for the construction of C=C bond with the reaction of aldehyde/ketone with phosphorous ylide. Using BH strategy, formation of alkane is possible directly from alcohol (Scheme **1.32**).



Scheme 1.32: Indirect Wittig reaction using alcohols.

William and co-workers[106] demonstrated iridium catalyzed dehydrogenation of alcohol to synthesize alkane *via* indirect Wittig reaction. After one year, they have also performed Ruthenium catalyzed indirect Wittig reaction to synthesized alkane.[107]

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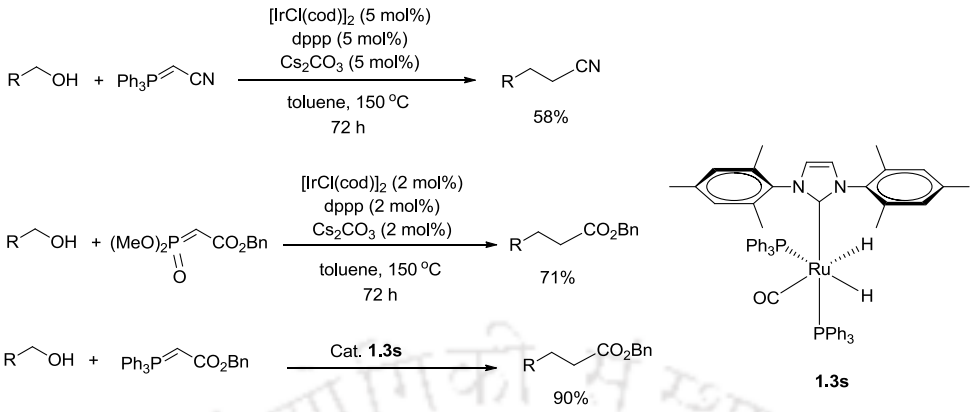
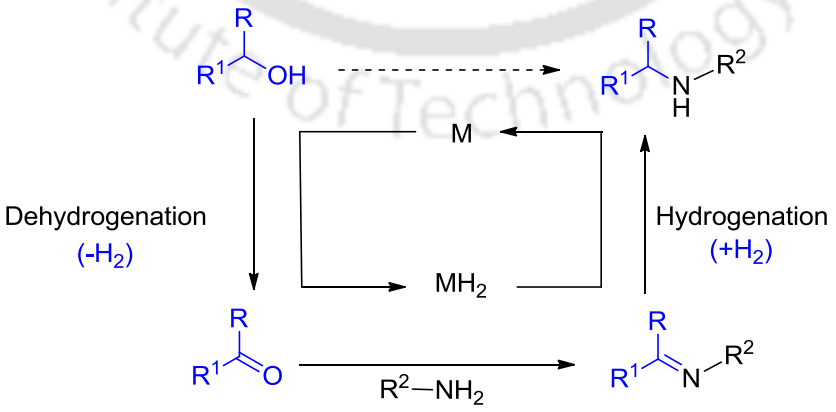


Scheme 1.33: Iridium and ruthenium catalyzed indirect Wittig reactions with phosphorus ylide.

1.3.1.2. C-N bond formation:

1.3.1.2a. Amination of alcohol:

Amination of alcohol using alcohol and amine *via* BH strategy have great advantages over conventional alkylation method.[108] In classical alkylation reaction, primary amine reacts with alkyl halide and produce secondary amine which is more reactive than primary amine and there is a high chance to over alkylation. BH approach not only minimizes the over alkylation but also it will minimizes the waste which is generated by the use hazardous reagents. The BH process takes place simultaneously three in situ successive reactions 1) dehydrogenation, 2) condensation and 3) hydrogenation (Scheme **1.34**).



Scheme 1.34: Amination of alcohol *via* Borrowing Hydrogen Reaction

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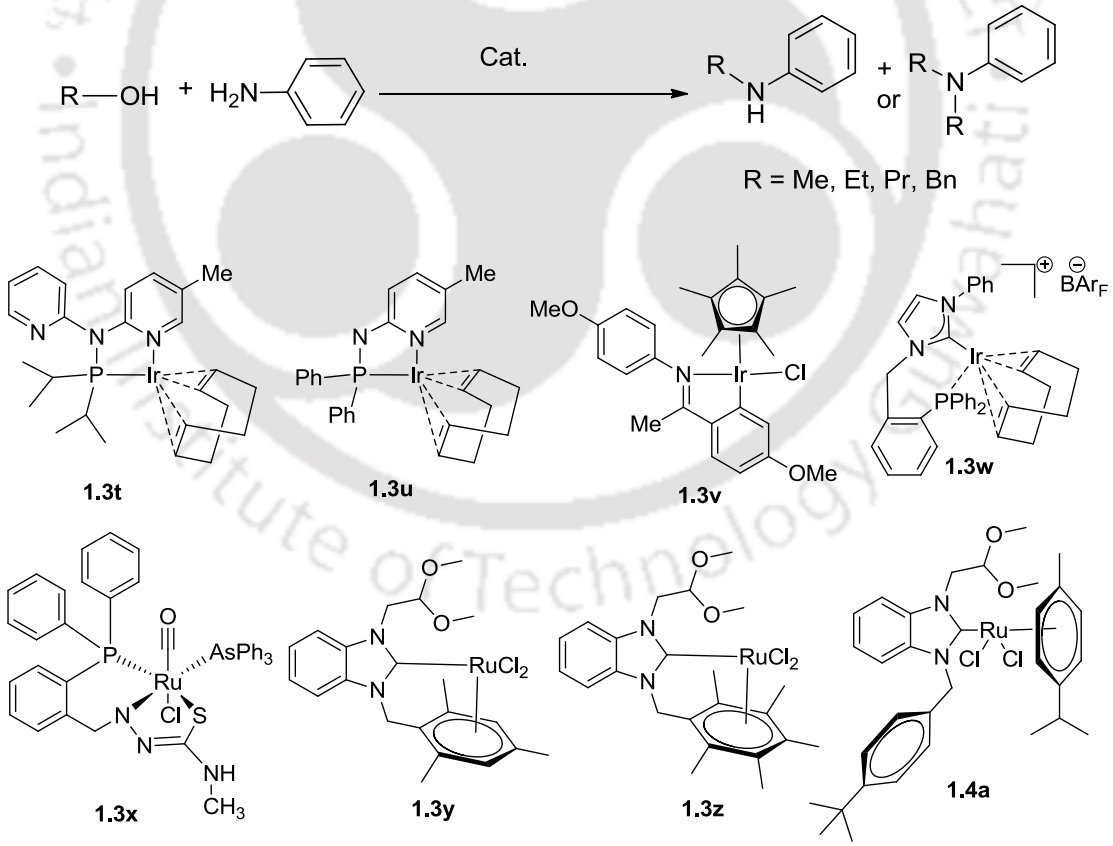
In 1981, *Grigg*[109] and *Watanable*[110] independently reported *N*-alkylation of amine with alcohol *via* BH strategy using $[RhH(PPh_3)_4]$ and $[Ru(PPh_3)_3Cl_2]$ catalyst respectively and found great activity towards this reaction. After that, again iridium and ruthenium complexes dominated in these types of transformation. $[Cp^*IrCl_2]_2$ complex can able to do this transformation very efficiently and was first reported by *Yamaguchi*[111] in 2003. In 2010, *Kempe*[112] reported that different types of aniline have been mono-alkylated with alcohol in the presence of complex **1.3u** and **1.3v** under mild reaction conditions 70 °C and a very low catalyst loading 0.05% (Scheme **1.35**). *Xiao and co- workers*[113] also demonstrated *N*-alkylation of amine with iridium complex **1.3v** by using catalytic amount of weaker base (5 mol% K_2CO_3). In 2013, *Andersson*[114] reported iridium-catalyzed **1.3w** selective alkylation of anilines with alcohols at room temperature and without solvent. A ruthenium-phosphine-based catalyst **1.3x** was active towards this transformation at very low catalyst loading and was reported by *Ramachandran et al.*[115]



Scheme 1.35: *N*-alkylation of amine with alcohol using Ir and Ru complexes

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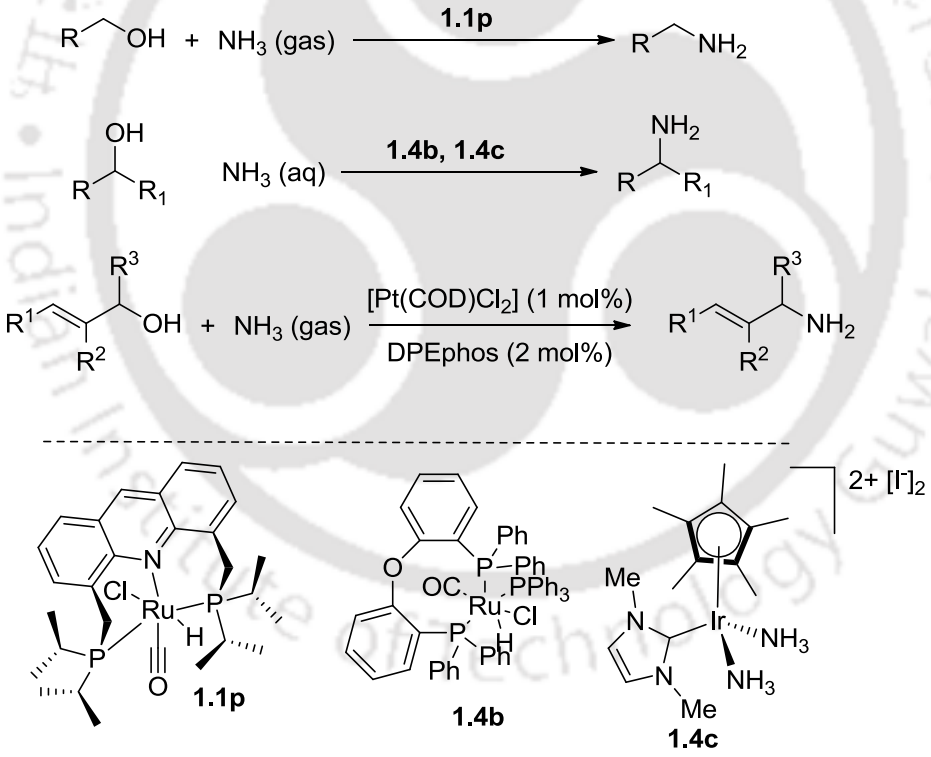
Ru-NHC complexes **1.3y**-**1.4a** efficiently did the *N*-alkylation reaction of different cyclo-aliphatic amines like pyrrolidine and morpholine with different benzylic alcohols and was reported by *Bruneau*.[116] In recent time, the capability of earth-abundant 3d transition metal complexes such as Mn,[117] Fe[118] and Co[119] has been explored to catalyse such type of reactions.

1.3.1.2b. *Amination of alcohol using ammonia:*

There is another well-known method to synthesize amine from alcohol using ammonia. The advantages of this reaction is, one can easily synthesize structurally important different amine in large scale as ammonia inexpensive and has high atom efficiency.



Scheme 1.36: The dehydrogenative amine synthesis from primary/secondary alcohol by noble metal catalyst.

First, *Milstein's group*[120] have studied the formation of primary amine using cheap ammonia by ruthenium acridine complex **1.1p**. Later on, *Baumann et al*[121]

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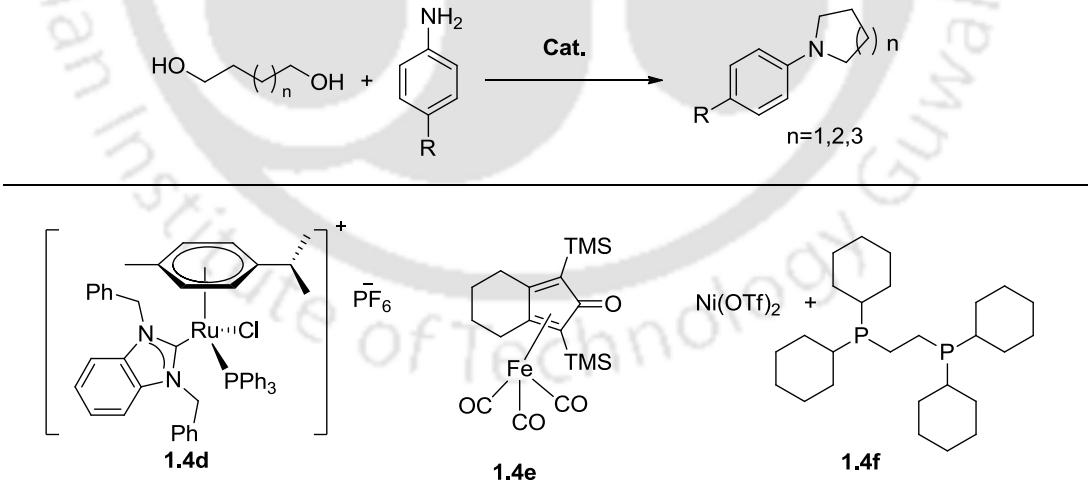
reported the same reaction with aqueous ammonia catalyzed by **1.4b**. After that, *Beller*[122] *and Vogt*[123] independently reported the synthesis of primary amines, by the reaction of ammonia and secondary alcohols using $Ru_3(CO)_{12}$/ CataCXiumPCy, with a variety of ligands system. In recent time, a water soluble NHC-Ir catalyst (**1.4c**) has been reported by *Yamaguchi*[124] towards this efficient transformation to produce amine by using secondary alcohol and aqueous ammonia. Selective synthesis of primary allylamine was also reported by *Mashima*[125] catalyzed by $Pt(cod)Cl_2$ complex using ally alcohol and aqueous ammonia (Scheme **1.36**).

1.3.1.2c. Synthesis of saturated N-heterocycles:

Saturated *N*-heterocycles are regarded as essential structural scaffolds, due to their presence in physiologically active molecules and pharmaceutical substances. A ruthenium complex **1.3.5e** was able to synthesize *N*-alkylated amines cyclic amines from amines with different diols[126] (Scheme **1.37**). Later, a wide range of *N*-heterocycles have been synthesize *via* borrowing hydrogen strategy with Fe[127] and Ni[128] catalyst (Scheme **1.38**).



Scheme 1.37: *N*-alkylation of amine with different diols using Ru complex

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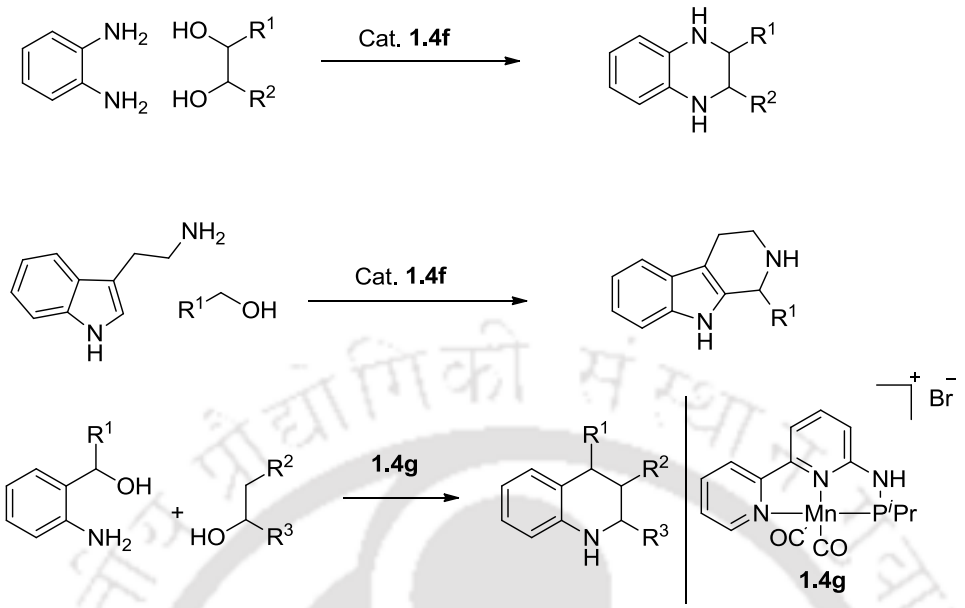

Scheme 1.38: Synthesis of saturated *N*-heterocycles

1.4. Concluding remarks:

Recently, acceptorless dehydrogenation and borrowing hydrogen principle have attracted much attention using pincer-based ruthenium complexes, because of their significant contribution to the creation of atom-economical, environmentally benign sustainable methodologies for the synthesis of important building blocks. The majority of these highly active metal complexes include phosphine pincer ligands based on pyridine, bipyridine, acridine, or diethyl amino. Although this phosphine based pincer ligands have shown significant applications in homogeneous catalysis, they have suffered from well-known drawbacks such as air and moisture sensitivity, as well as cost-effectiveness. Thus, the hunt for novel air-stable pincer ligands with catalytic potential has piqued our interest. In this regard, we synthesized new air- and moisture-stable NNS- and SNS ruthenium pincer complexes and investigated their catalytic applicability towards acceptorless dehydrogenation and borrowing hydrogen reaction.

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Chapter 2

Acceptorless Dehydrogenative Construction of C=N and C=C bond through Catalytic Aza-Wittig and Wittig Reaction in the Presence of Air-stable Ruthenium Pincer Complex

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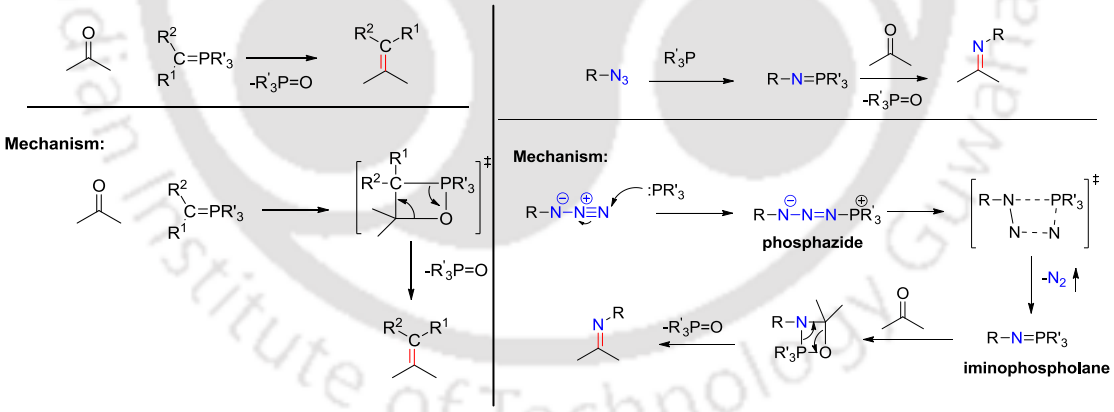
2.1. Introduction:

In this chapter, I have mainly discussed the synthesis of new air stable SNS- and NNS-Ru-complexes and explored their applicability in acceptorless dehydrogenation reaction. Acceptorless dehydrogenative catalytic aza-Wittig and Wittig reaction was performed using these catalysts under very mild reaction conditions. The synthesis of imine, alkene and structurally important pyrrolo[1,4] benzodiazepines derivatives were achieved using these complexes.

The Wittig reaction[1], also known as Wittig olefination, is a chemical reaction that occurs when an aldehyde or ketone reacts with a Wittig reagent, which is a triphenyl phosphonium ylide ($R_2C=PR_3$) (Scheme **2.1**, left). It is the most important carbon-carbon bond forming transformations in organic chemistry under mild reaction condition. After the discovery of Wittig reaction, Staudinger and Meyers reported the synthesis of phosphazines, ($R\text{-}N=PR_3$) that have been applied in the construction of C=N bonds with an aldehyde or ketone, and become popular as aza-Wittig reaction[2] (Scheme **2.1**, right).



Scheme 2.1: Wittig (left) and aza-Wittig (right) reaction and mechanism

Since then, the Wittig and aza-Wittig reactions have experienced remarkable development and become a powerful tool for the construction of nitrogen-containing heterocycles (Scheme **2.2**).[3] For example, precursor of adenophorine,[3d] a rare example of a naturally occurring azasugar with hydrophobic substituents have been

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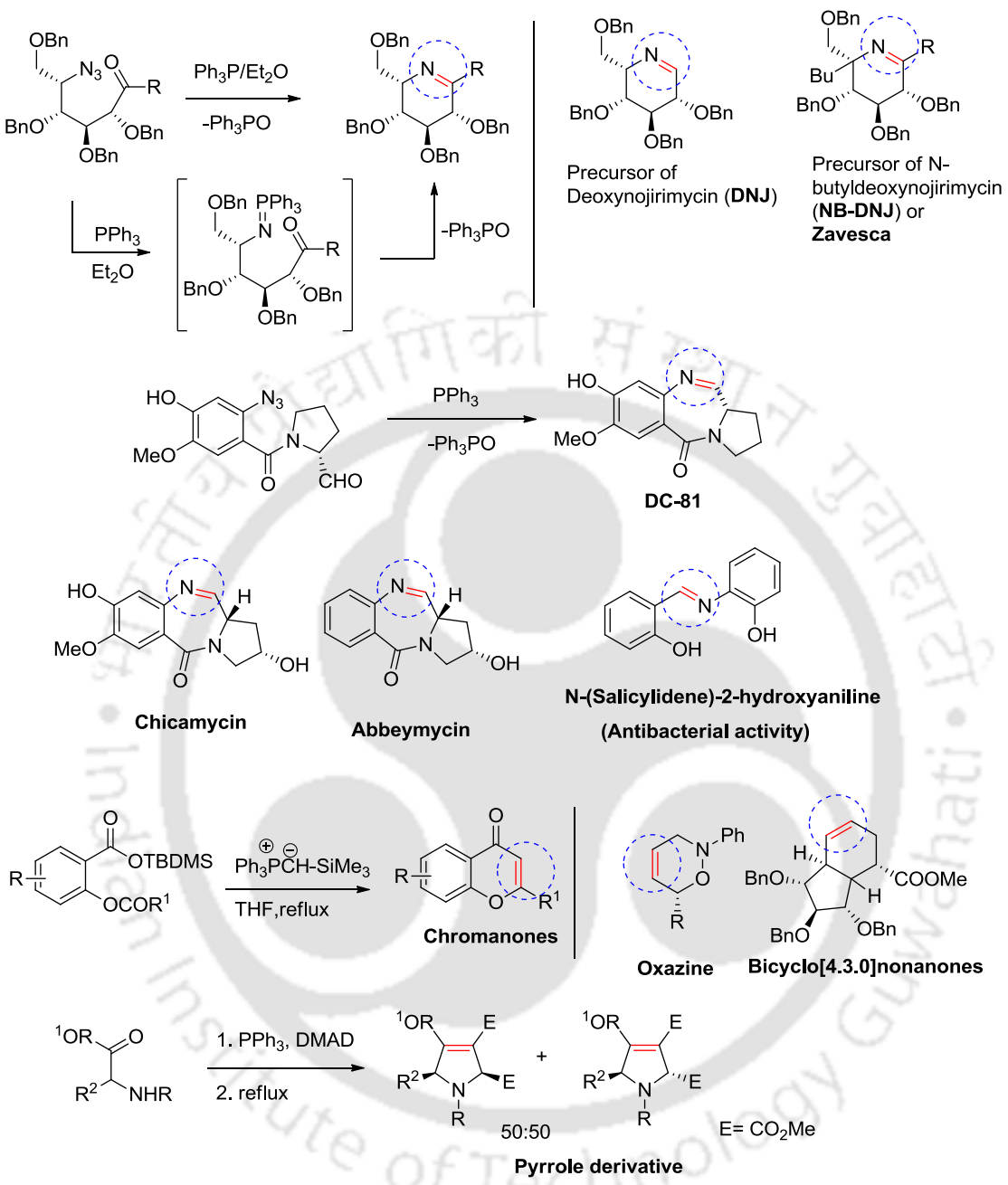

Scheme 2.2: Heterocycle molecule containing C=N and C=C bond through Wittig and aza-Wittig reactions

synthesized through the Staudinger/aza-Wittig sequence as shown in Scheme **2.2**. The same strategy has been applied for the preparation of the antibiotic DC-81[3e] by intramolecular reductive cyclization with polymer-supported triphenylphosphine. A

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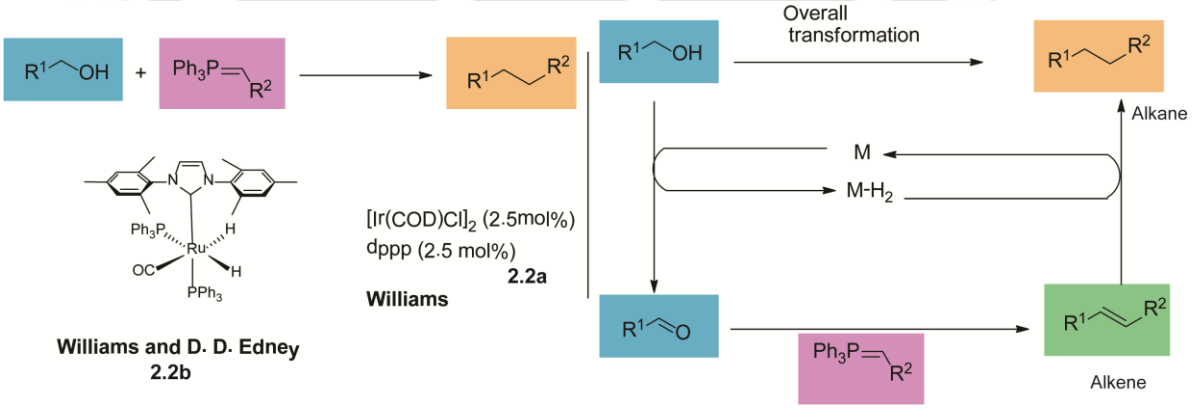
series of chromanones[8f] and heterocycles[8g,8h] were synthesized by application of the intramolecular Wittig ring closure and intermolecular Wittig reaction.

The Wittig and aza-Wittig reaction required a carbonyl functionality to form corresponding products. De(hydrogenative) Wittig and aza-Wittig reaction directly from the renewable alcohols have recently attracted the attention of the scientific communities. In this type of reaction, there is a possibility of the formation of C=C and C=N bond *via* acceptorless dehydrogenation or the formation of C-C and C-N single bond *via* borrowing hydrogen catalysis. Different catalyst and reaction conditions have been employed to obtain the desired selectivity.

An effective 'borrowing hydrogen method to synthesize alkane directly from alcohol, through indirect Wittig reaction catalyzed by iridium or ruthenium complex, was first developed by William and co-workers[4] (Scheme **2.3**). The mechanism involved in indirect Wittig reaction is represented in Scheme **2.3**. First alcohol can be dehydrogenated by complex to form more active carbonyl compound, which will undergo olefination with phosphorous ylide.



Scheme 2.3: Indirect Wittig reaction of alcohols by catalytic electronic activation

After that, the intermediate alkene undergoes hydrogenation reaction to provide the alkane product. Here, the hydrogen atom "borrowed" during dehydrogenation step and return to alkene intermediate for hydrogenation. So, this strategy provides alkane derivatives directly from alcohol and potentially offers an efficient alternative route

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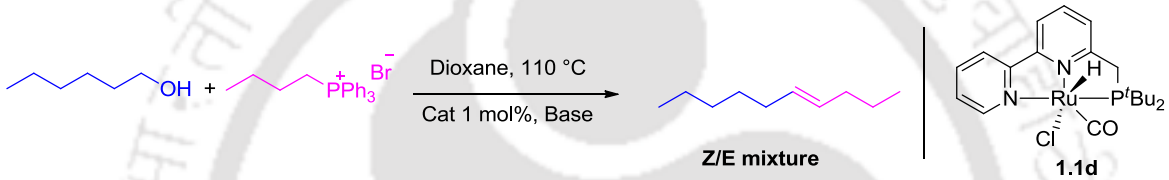
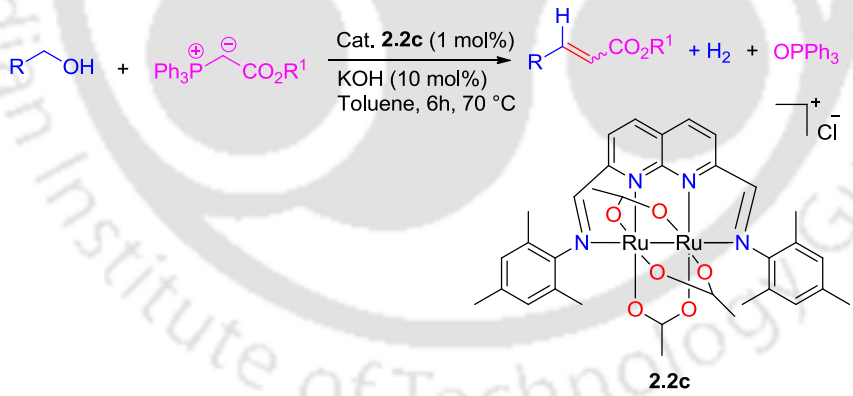
rather than the traditional route involving multistep strategies using hazardous reagents and lengthy work-up procedures, which generates a large amount of waste.

Recently, Milstein and co-workers[5b] have shown the selective synthesis of alkene[6] directly from alcohol through catalytic oxidant-free Wittig reaction[5] in presence of phosphine based-ruthenium pincer complex (Scheme **2.4**). The reaction uses low catalyst loadings and the reaction leads to Z (aliphatic) or E (benzylic) stereospecificity.

In 2016, *J.K. Bera*[5a] group developed a diruthenium(II,II) **2.2c** complex catalyzed one-pot reaction with alcohols and triphenylphosphonium ylides afforded the corresponding olefins in high yields with excellent E selectivity (Scheme **2.5**).



Scheme 2.4: First reaction demonstrating the validity of the olefination of alcohols using Wittig reagents



Scheme 2.5: Catalytic olefination of alcohols by **2.2c** using Wittig reagent

A few years ago, William and co-worker[7] developed a method to convert alcohols into *N*-alkyl anilines *via* aza-Wittig type reaction in presence of iridium catalyst (Scheme **2.6**), where the formed imine hydrogenate in-situ by the catalyst and formed secondary amine as a major product. They also showed that under mild reaction conditions indirect aza-Wittig reaction gives better yield to form *N*-alkyl anilines than the *N*-alkylation

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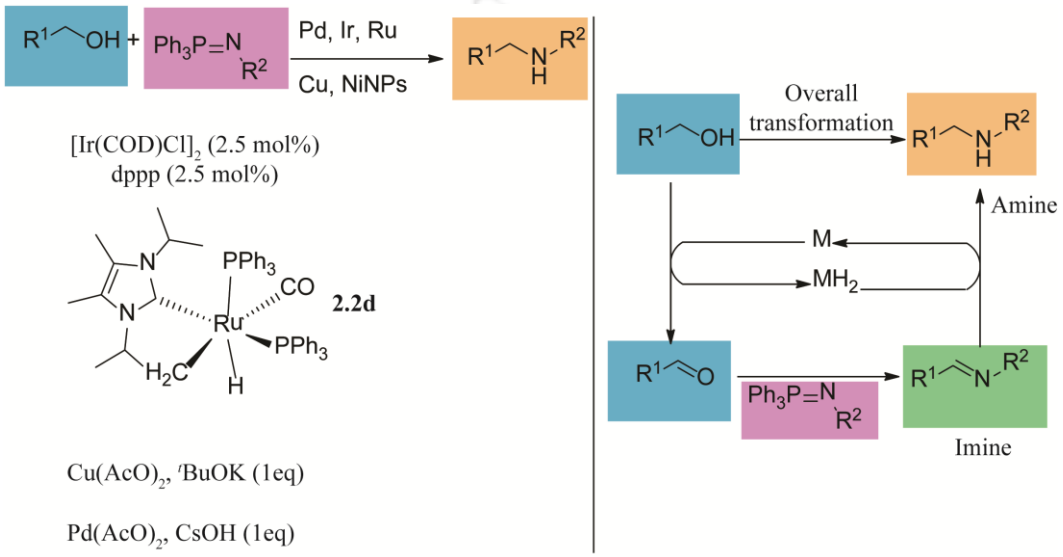
reaction of aniline. After that in 2008, indirect aza-Wittig reaction was reported using NiNPs[8a] and gave a moderate yield. In 2011, *Ramon and co-worker* successfully did *N*-alkylation of amine using indirect aza-Wittig reaction using $Pd(OAc)_2$[8b] and $Cu(OAc)_2$[8c] with high loading of bases.



Scheme 2.6: Indirect aza-Wittig reaction of alcohols by homogeneous catalyst

It would be significant if the selective synthesis of imine can be achieved *via* aza-Wittig reaction as C=N bond containing molecules are known for their various biological importance. So, the selective formation of C=N bond[9] and C=C bond directly from alcohol through catalytic aza-Wittig and Wittig reaction under mild reaction conditions is important and would be a significant advance.

2.2. Present work:

Chapter 2 discusses the synthesis, purification and characterization of SNS and NNS ligand derived Ru-complexes. The efficacy of the new ruthenium complexes was examined towards *C=N and C=C* bond formation by the dehydrogenative coupling of

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alcohol and azide/Wittig-salt *via* aza-Wittig/Wittig type reaction. Furthermore, the synthesis of structurally important pyrrolo[1,4]benzodiazepines derivatives has also been achieved by the use of this methodology.

2.2.1. Synthesis of SNS-Ru complexes and their characterizations:

First, the acridine-based SNS ligand was prepared by nucleophilic substitution reaction of 4,5-bis(bromomethyl)acridine with the corresponding thiolate.[10] The complex **2.1A** was synthesized by stirring $RuCl_2(PPh_3)_3$ with the ligand in CH_2Cl_2 for 12 h. The brown colored single crystal suitable for X-ray diffraction was developed by layering the solution of the complex **2.1A** in a mixture of dichloromethane and acetonitrile with diethyl ether under air. Crystal structure (Figure **2.2**) showed the geometry of the Ru center to be pseudo-octahedral type with an elongated Ru-N bond (2.56 Å). This bond length is slightly longer than the one observed in case of acridine PNP based ruthenium pincer complex reported by Milstein (Ru-N: 2.479 Å)[13c] or Hofmann (Ru-N: 2.488 Å).[11]

The complexes **2.2A** and **2.3A** were prepared by refluxing the $RuCl_2(PPh_3)_3$ with the corresponding tridentate ligand in THF. ^{1}H- and ^{31}P{1H}-NMR spectral analysis reveals that the complex **2.2A** exists as one pure isomer in solution whereas complex **2.3A** exists in solution as an isomeric mixture (60:40) at room temperature. The complex **2.2A** and **2.3A** were crystallized by layering their solution in $CHCl_3$ with diethyl ether and hexane respectively at ambient temperature. The solid-state structure of both **2.2A** and **2.3A** was found to be *trans-(meri-)* dichloride complex (Figure **2.1**).

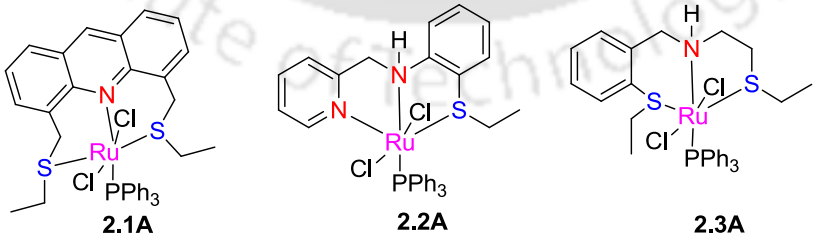

Figure 2.1: Ruthenium complexes

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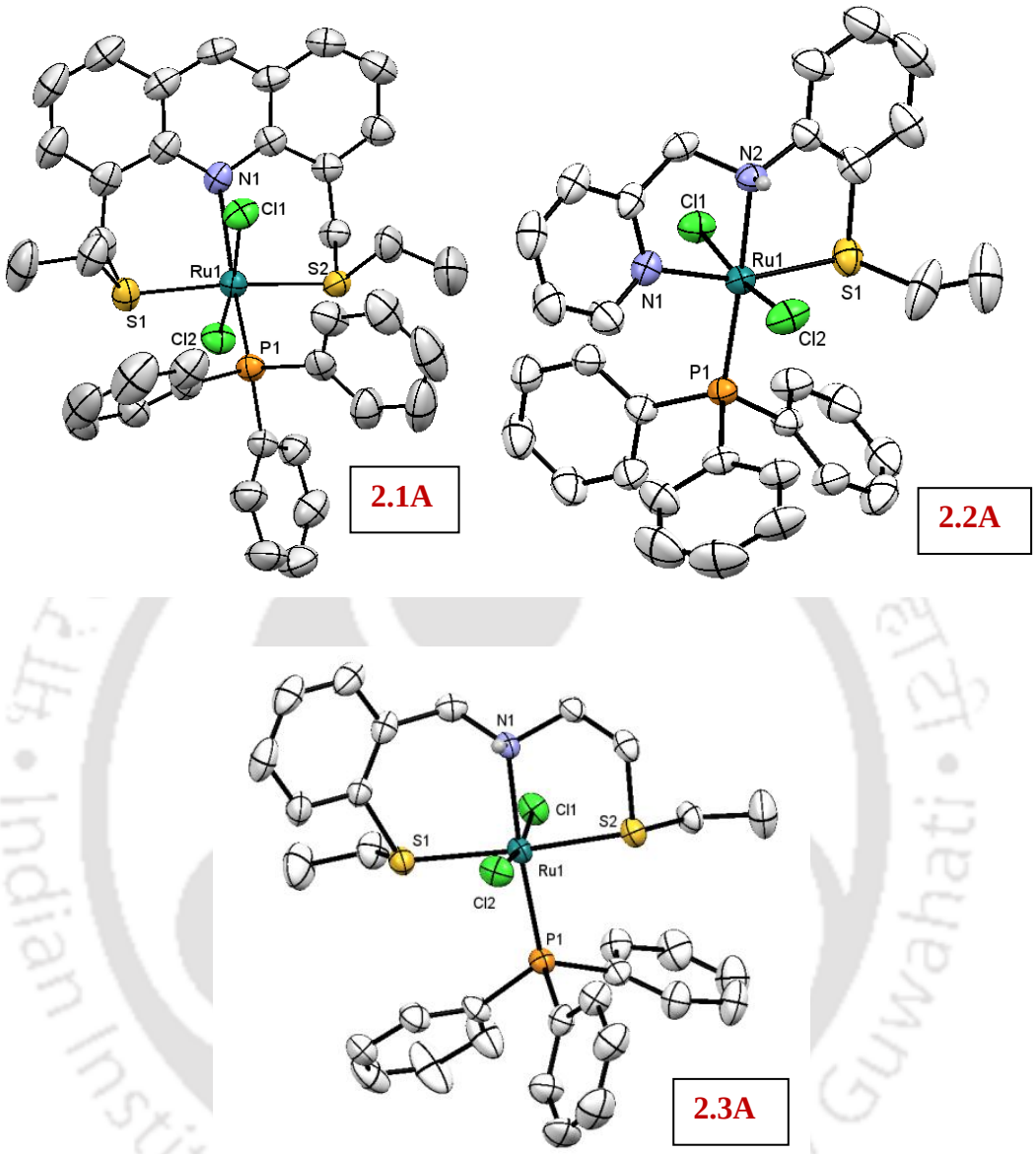

Figure 2.2: Molecular structure of complex **2.1A** (thermal ellipsoid 50% probability level), **2.2A** and **2.3A** (thermal ellipsoid 30% probability level) (for the clarity, all hydrogens except nitrogen are omitted)

The Ru-complexes were characterised by spectroscopic analyses such as NMR (^{1}H and ^{13}C) and ESI-mass spectrometry (experimental section). The formation of the complexes was further confirmed by single crystal X-ray structure determination. The crystallographic data (experimental section) and ORTEP diagram of complex **2.1A**, **2.2A** and **2.3A** are shown in Figure **2.2**. The crystal structure of complex **2.1A** is more like pseudo octahedral geometry around Ru-center which is connected through two S atoms

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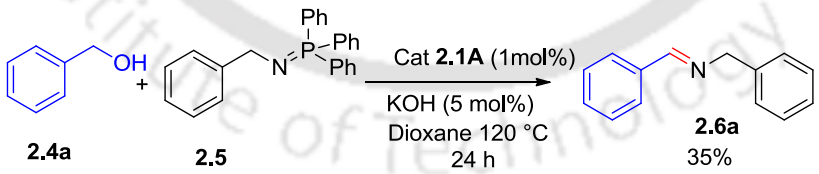
and one N atom from the ligand and two chlorine and one triphenylphosphine group. The crystal structure of three complexes reveal that both chlorine atoms are *trans* to each other and the triphenylphosphine group are *trans* to the N atom and found to be *trans-(meri-)* dichloride complex.

After complete characterization, these Ru-complexes were applied for acceptorless dehydrogenative catalytic aza-Wittig and Wittig reaction through acceptorless dehydrogenation to synthesized imine and alkene using alcohol.

2.2.2. Optimization of reaction conditions:

Initially, the catalytic activity of the complexes towards the synthesis of imines directly from alcohol and phosphazines was investigated. To explore the feasibility of the catalytic aza-Wittig reaction, a dioxane solution containing benzyl alcohol (1 mmol) and $PhCH_2N{=}PPh_3$ (1 mmol) was refluxed at 120 °C (bath temperature) for 24 h in presences of 0.01 mmol of complex **2.1A** and 0.05 mmol of KOH under argon atmosphere. 35% (E)-N-benzylidene-1-phenylmethanamine was isolated (Scheme **2.7**). Encouraged by the initial attempt, I thought to prepare the aza-Wittig reagent in situ. Thus a mixture of benzyl alcohol (1 mmol), benzyl azide (1 mmol) and triphenyl phosphine (1 mmol) in dioxane (5 mL) was refluxed (bath temperature 120 °C) in presence of 0.01 mmol of complex **2.1A** and 0.05 mmol of KOH 36% (E)-N-benzylidene-1-phenylmethanamine was obtained after 24 h and 64% benzyl alcohol remained unreacted (Table **2.1**, entry **1**).



Scheme 2.7: Catalytic oxidant free aza-Wittig reaction in presence of acridine SNS based ruthenium pincer complex

As the reaction showed similar activity, I decided to proceed further through the protocol with *in situ* generated phosphazine. Thus, when toluene was used as a solvent, 46% desired imine was formed only after 18 h (Table **2.1**, entry **2**). Upon increasing the

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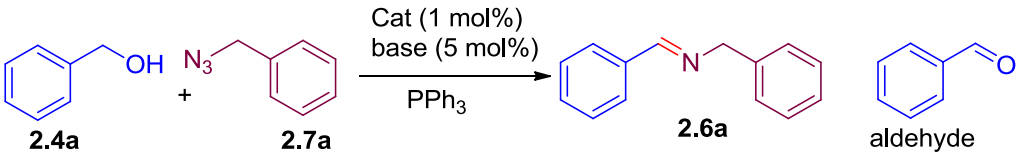
Table 2.1: Optimization of the reaction condition for the catalytic aza-Wittig reaction.[a]



2.4a **2.7a** **2.6a** aldehyde

Entry	Cat.	Base	Solvent	Bath temperature (°C)	Time (h)	Yield[b] [%]	aldehyde[b] [%]
1	**2.1A**	KOH	Dioxane	120	24	36	-
2	**2.1A**	KOH	Toluene	120	18	46	-
3	**2.1A**	**KOH**	**Toluene**	**135**	**18**	**91**	**3**
4	**2.2A**	KOH	Toluene	135	18	30	-
5	**2.3A**	KOH	Toluene	135	18	60	-
6	**2.1A**	-	Toluene	135	18	trace	-
7	**2.1A**	^{t}BuOK	Toluene	135	18	52	5
8	**2.1A**	K_2CO_3	Toluene	135	18	43	-
9	**2.1A**	KOH	THF	76	24	10	-
10	**2.1A**	KOH	Et_2O	55	24	5	-
11	**2.1A**	KOH	Toluene	135	4	52	-
12[c]	**2.1A**	KOH	Toluene	135	36	70	-
13	[(p-Cymene) $RuCl_2]_2$	KOH	Toluene	135	24	27	-
14	$RuCl_2(PPh_3)_3$	KOH	Toluene	135	24	30	-
15[d]	**2.1A**	KOH	Toluene	135	24	83	10
16	**2.1A**	KOH	Toluene	110	18	30	-

[a]Reaction conditions: benzyl alcohol (1 mmol), benzyl azide (1 mmol), PPh_3 (1 mmol), solvent (5 mL).
[b]NMR yield using dioxane or CH_3CN as internal standard. [c]0.5 mol% catalyst loading. [d] under air.

reaction temperature (bath temperature 135 °C), the yield of the desired (E)-N-benzylidene-1-phenylmethanamine was improved to 91% with the complete consumption of benzyl alcohol as indicated by NMR. Pure imine was obtained (87%) after column chromatography. Under similar reaction conditions, complexes **2.2A** or **2.3A** gave an inferior yield of the desired imine (Table **2.1**, entries **4** and **5**). The catalyst failed to give any desired imine without a catalytic amount of base (Table **2.1,** entry **6**). The effect of the base has been studied and KOH is found more effective than ^{t}BuOK or

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K_2CO_3 (Table **2.1,** entries **7** and **8**). The reaction was not going well in THF and diethyl ether as solvent (Table **2.1**, entries **9** and **10**). However, when 0.05 mol% of catalyst **2.1A** was used, keeping other conditions unaltered, only 70% desired imine was obtained after 36 h (Table **2.1,** entry **12**). The reaction under air gave 83% yield of the desired imine, which was slightly lower compared to the inert reaction condition (Table **2.1**, entry **15**). Under the similar conditions, $[(p\text{-Cymene})RuCl_2]_2$ or $RuCl_2(PPh_3)_3$ gave substantially lower yield of the desired product (Table **2.1**, entries **13-14**). Lowering the bath temperature to 110 °C, the desired imine was obtained 30% in toluene (Table **2.1**, entry **16**).

2.2.3. Substrate scope of aza-Wittig reaction:

To study the scope of the reaction with respect to aromatic azides, the optimized reaction conditions were applied to the reaction of benzyl alcohol and phenyl azide. 85% yield of the desired (E)-*N*-benzylidenebenzenamine was obtained after 18 h (Scheme **2.8**, entry **2**). Encouraged by this result, the scope of the reaction has been extended. Thus, the reactions of differentially substituted benzyl alcohol with variously substituted aromatic or benzyl azide were studied. It has been observed that both electron-withdrawing and electron-donating substituents in the aromatic ring gave excellent yield in this catalytic dehydrogenative aza-Wittig reaction methodology. Exploring the scope of the reaction with regard to secondary alcohol, 1-phenylethanol was reacted with phenyl azide. The yield of the desired imine was 65% (Scheme **2.8**, entry **14**) even after 48 h, which is probably due to the lower reactivity of ketones towards the aza-Wittig reaction. In this reaction, 35% of acetophenone was also observed. Secondary azide, reacting with benzyl alcohol also gave a moderate yield (54%). Delightfully, no dehalogenation reaction was observed when 4-chlorobenzyl alcohol or 4-bromobenzyl alcohol was used as substrates. It is interesting to note that 75% of (E)-N-(2-aminobenzylidene)benzenamine were achieved when 2-amino benzyl alcohol was reacted with 2 equivalents of phenyl azide and triphenyl phosphine (Scheme **2.8**, entry **16**). 2-Nitrobenzylzlcohol and phenyl azide gave (E)-N-(2- nitrobenzylidene)

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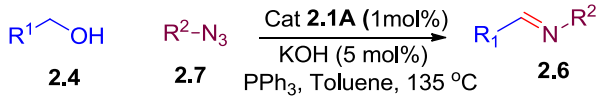
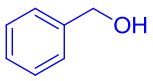
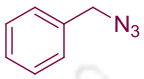
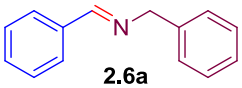
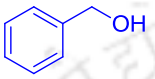
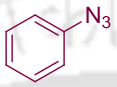
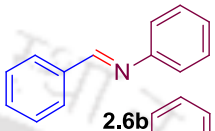
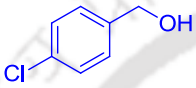
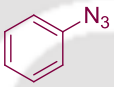
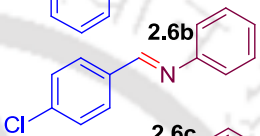
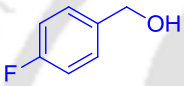
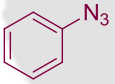
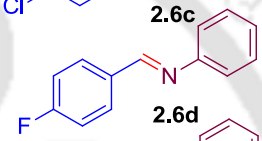
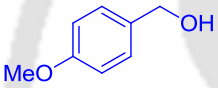
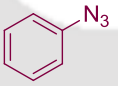
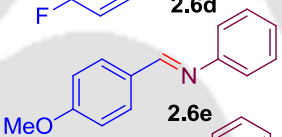
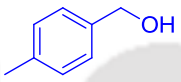
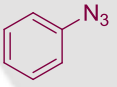
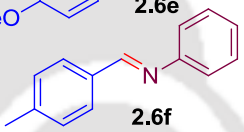
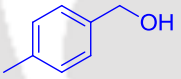
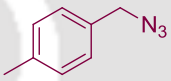
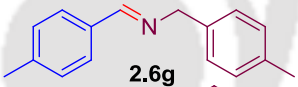
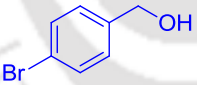
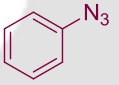
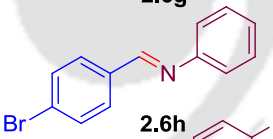
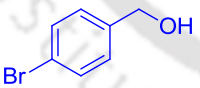
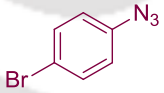
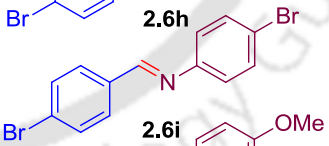
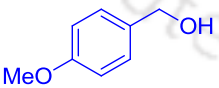
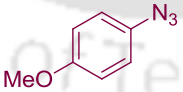
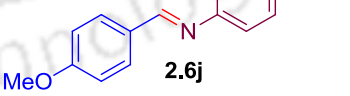
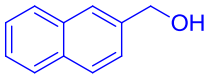
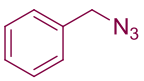
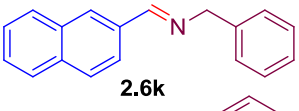
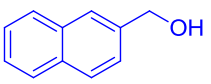
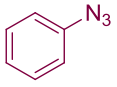
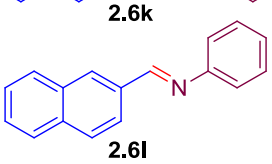


2.4 **2.7** **2.6**

R^1, R^2= alkyl,aryl,aliphatic, heteroaryl

Entry	Alcohol	Azide	Product	Yield[b] (%)
1			 **2.6a**	91(87)
2			 **2.6b**	85(80)
3			 **2.6c**	90(85)
4			 **2.6d**	87(80)
5			 **2.6e**	87(84)
6			 **2.6f**	(86)
7			 **2.6g**	(84)
8			 **2.6h**	(80)
9			 **2.6i**	(82)
10			 **2.6j**	(85)
11			 **2.6k**	(90)
12			 **2.6l**	(88)

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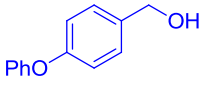
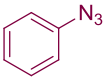
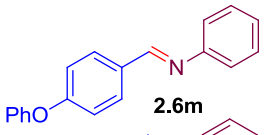
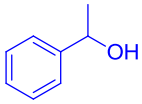
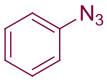
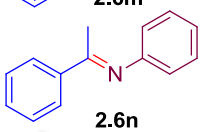
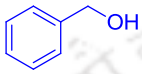
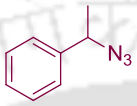
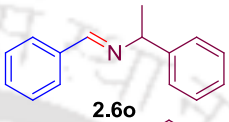
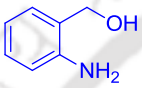
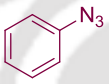
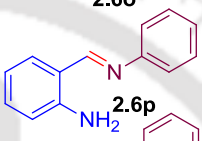
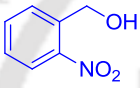
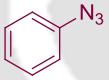
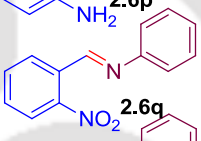
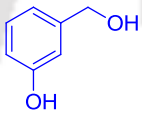
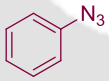
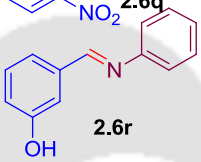
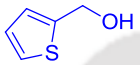
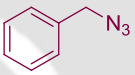
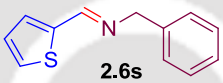
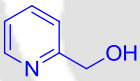
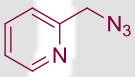
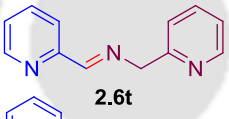
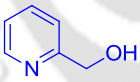
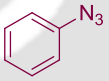
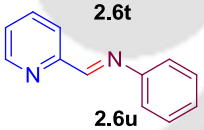
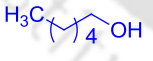
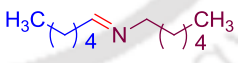
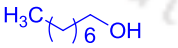
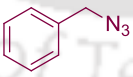
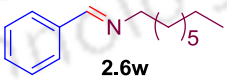
Entry	Alcohol	Azide	Product	Yield[b] (%)
13			 **2.6m**	91
14[c]			 **2.6n**	65(55)
15			 **2.6o**	(54)
16[d]			 **2.6p**	(75)
17			 **2.6q**	(74)
18			 **2.6r**	(80)
19			 **2.6s**	(79)
20			 **2.6t**	(60)
21			 **2.6u**	(65)
22[e]			 **2.6v**	83(68)
23			 **2.6w**	(65)

Scheme 2.8: Catalytic aza-Wittig type reaction directly from alcohol and azide.[a] [a]Reaction conditions: alcohol (1 mmol), benzyl azide (1 mmol), PPh_3 (1mmol), toluene (5 mL), cat **2.1A** (1 mol%), KOH (5 mol%). [b]NMR yield, the yield in the parenthesis-isolated yield. [c]48 h. [d]Phenyl azide (2 mmol), PPh_3 (2 mmol). [e]24 h.

benzenamine in 74% yield. A small amount (15%) of (E)-N-(2-aminobenzylidene) benzenamine was also obtained due to the reduction of the nitro group under the reaction

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condition (Scheme **2.8**, entry **17**). The reaction methodology was successfully extended to heterocyclic alcohols; both 2-thiophenemethanol and 2-pyridinemethanol gave moderate to good yields of the desired imine under the optimized reaction conditions. To expand the scope of the reaction with regard to aliphatic alcohols or aliphatic azide, the optimized reaction conditions were applied to the reaction of hexanol with hexyl azide. An excellent yield (83%) of the desired imine was obtained only after 24 h (Scheme **2.8**, entry **22**). Similarly, octanol reacted smoothly with benzyl azide to give a mixture of (E)-N-octyl-1-phenylmethanimine (71%) and (E)-N-benzyloctan-1-imine (14%). Here the initially formed (E)-N-benzyloctan-1-imine was isomerized to form the more stable (E)-N-octyl-1-phenylmethanimine under the reaction conditions and has been isolated (65%).

2.2.4. Plausible catalytic cycle.

We proposed a probable mechanism for the indirect aza-Wittig reaction with primary alcohols as shown in Scheme **2.9**. In the initial step, in presence of base and addition of alcohol, complex **2.1A** is converted ruthenium hydride species (**IV**) and the corresponding carbonyl compound. After that, alcohol coordination happened to the ruthenium centre and forms the complex **V**. After that removal of H_2 and aldehyde molecule, complex **IV** is regenerated and the cycle will continued. In the mean time, the in situ iminophospholane was formed from azide and triphenylphosphene and dehydrogenation of alcohol happened to form aldehyde or ketone. Next, the generated iminophospholane would undergo an aza-Wittig reaction with aldehyde or ketone to give the corresponding imine (Scheme **2.9**).

2.2.5. Control experiments:

To understand whether the reaction is going through the aza-Wittig type reaction pathway or through the *in situ* formation of amine[12] by hydrogen auto-transfer reaction, the reaction of 4-methoxy benzyl alcohol and benzyl azide was performed in the absence of PPh_3. Only 40 % desired imine was observed together with 56% of (E)-N-

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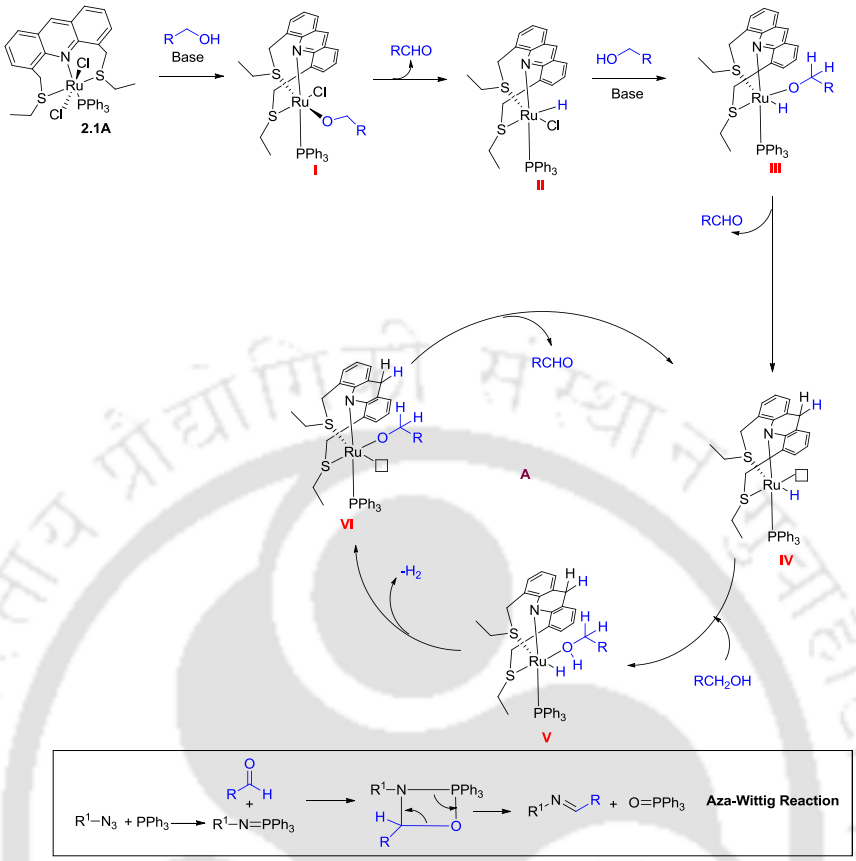
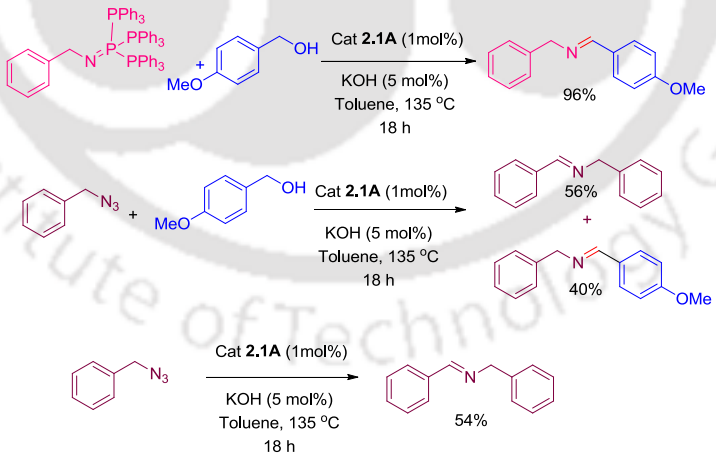


Scheme 2.9. Plausible mechanism



Scheme 2.10. Control experiments

benzylidene-1-phenylmethanamine (Scheme **2.10**). Next, the benzyl azide was treated with the catalyst **2.1A** and base, under the same reaction conditions and it was observed that the formation of (E)-N-benzylidene-1-phenylmethanamine (54%) was formed.[13] In

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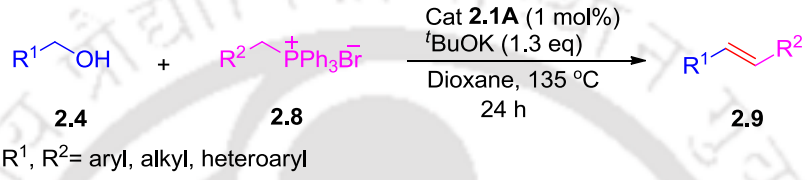
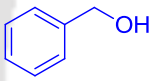
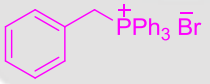
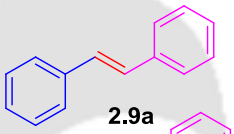
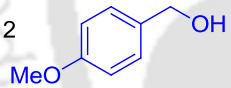
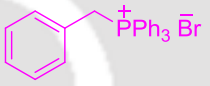
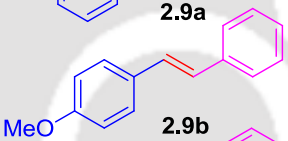
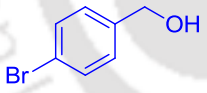
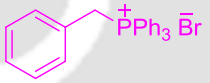
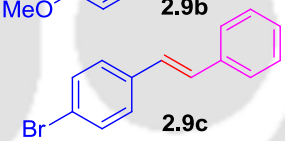
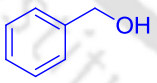
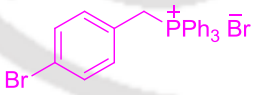
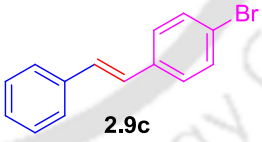
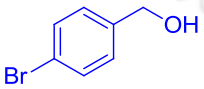
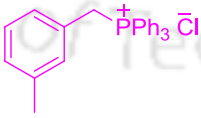
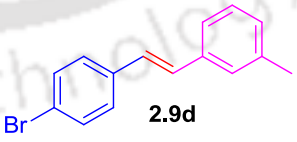
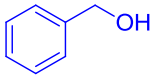
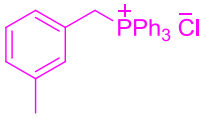
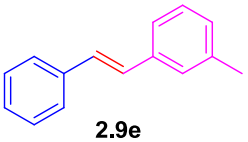
sharp contrast, the reaction of (benzylimino)triphenylphosphorane with 4-methoxybenzyl alcohol under the optimized reaction condition gave an excellent yield (96%) of the desired imine. Thus, we can conclude that the reaction was proceeding mainly through the aza-Wittig type reaction pathway *via* the rapid *in situ* formation of the aza-Wittig reagent.

2.2.6. Substrate scope of catalytic Wittig reaction:



Entry	Alcohol	Wittig Salt	Product	Yield (%)[b]
1			 2.9a	75
2			 2.9b	86
3			 2.9c	88
4			 2.9c	90
5			 2.9d	80
6			 2.9e	83

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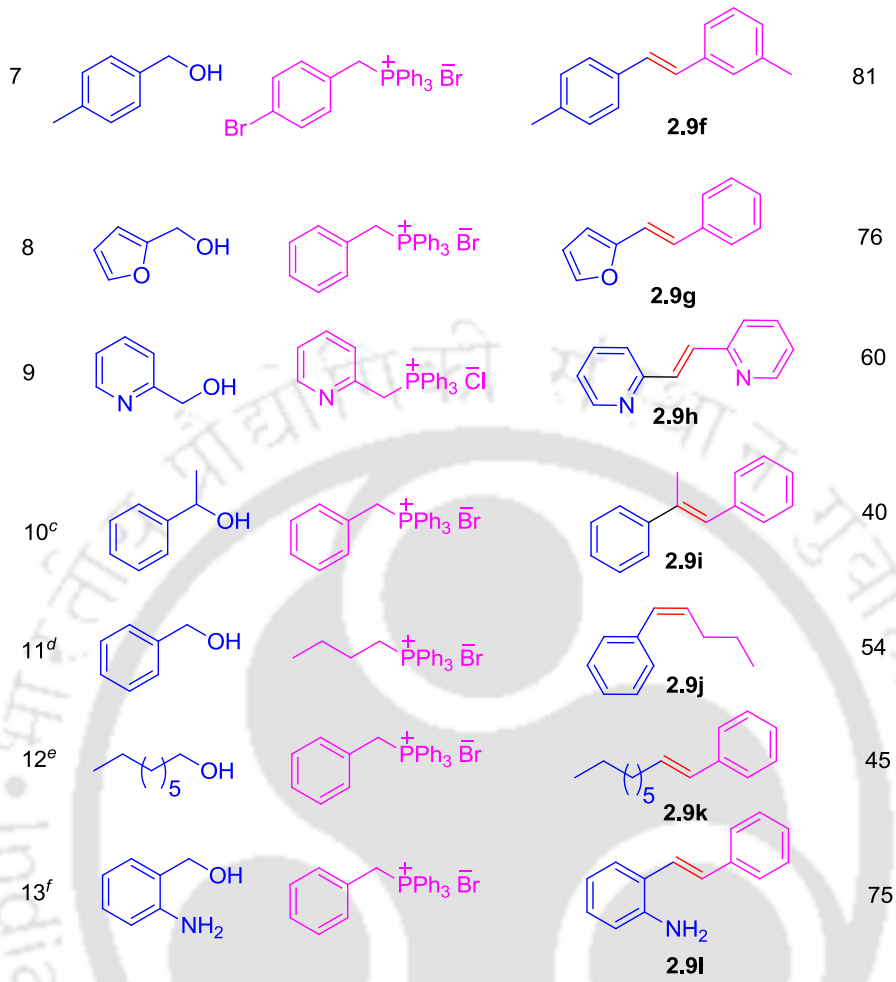

Scheme 2.11: Catalytic Wittig type reaction directly from alcohol and Wittig salt. [a]Reaction conditions: alcohol (1 mmol), phosphonium salt (1.2 mmol), dioxane (5 mL), cat **2.1A** (1 mol%), [t]BuOK (1.3 mmol). [b]Isolated yield, [c]E/Z 54:46, acetophenone left (35%). [d]E/Z 30:70, [e]48 h, [f]Wittig salt (2 mmol).

Next, the catalytic activity of the Ru-complex was investigated towards the oxidant-free Wittig reactions of alcohols for the construction of C=C bond. Scheme **2.11** summarizes the ruthenium catalyzed olefination reaction between alcohol and Wittig-salt. The reaction works well with different benzylic or heteroaryl alcohols and in most of the cases the E isomer is the major product together with a very small amount of Z product (1-2 %). The reaction is slower and moderate yield was obtained when aliphatic alcohol or aliphatic phosphonium salt was used as substrates (Scheme **2.11**, entries **11** and **12**). ^{1}H NMR analysis of the crude mixture of the reaction between

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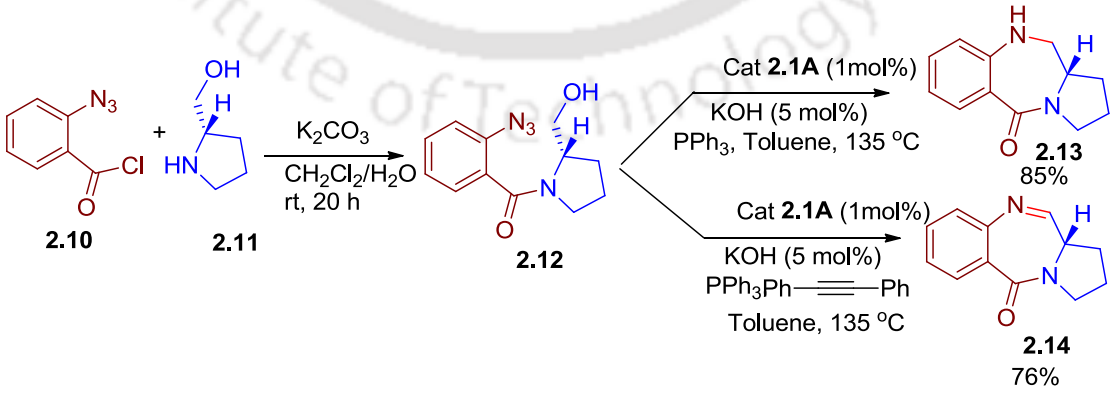
butyltriphenylphosphonium bromide with benzyl alcohol and 1-phenyl ethanol showed that E:Z isomers were formed in 30:70 ratio.

2.2.7. Structurally important pyrrolo[1,4]benzodiazepines (PBDs) synthesis:

Finally, I tried to apply this methodology to synthesize structurally important heterocyclic compounds. There is a wide range of biologically important compounds having pyrrolo[1,4]benzodiazepines (PBDs) as a core structural unit.[14] Thus, the scope of our protocol was examined for the synthesis of PBDs. (S)-(2-azidophenyl)(2-(hydroxymethyl) pyrrolidin-1-yl)methanone **2.12** was synthesized by the reaction of 2-azidobenzoyl chloride and L-prolinol. When a toluene solution containing 1:1 mixture of (S)-(2-azidophenyl)(2-(hydroxymethyl) pyrrolidin-1-yl)methanone and triphenylphosphine was refluxed in the presence of 1 mol% cat **2.1A**, 5 mol% KOH, (S)-1,2,3,10,11,11a-hexahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-5-one was obtained after 20 h (Scheme **2.12**). Interestingly no racemization was observed as the reaction was performed under almost neutral reaction condition. The imine formed was hydrogenated *in situ* to the corresponding amine **2.13**. Thus to obtain (S)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-5-one, **2.14**, (S)-(2-azidophenyl)(2-(hydroxymethyl)pyrrolidin-1-yl) methanone, **2.12** have been treated with equimolar amount of triphenylphosphine in the presence of 0.01 mmol of KOH and diphenyl acetylene as H_2 acceptor. Gratifyingly, a good yield of the desired product was obtained.



Scheme 2.12: Application of catalytic aza-Wittig reaction to synthesize benzodiazepines derivatives.

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2.3. Conclusions:

In conclusion, a catalytic route for the formation of C=N bond directly from alcohol and azide have been developed. The reaction strategy involves in situ preparation of aza-Wittig reagent and dehydrogenative coupling of aza-Wittig reagent with alcohol in presence of acridine derived air stable ruthenium pincer complex. This reaction showed a wide range of substrate scope. This efficient method has also been applied to the olefination reaction of alcohol and phosphonium salt. As a highlight, this protocol successfully applied to the synthesis of structurally important pyrrolo[1,4] benzodiazepines.

2.4. Experimental section:

General information

Unless otherwise mentioned, all the chemicals were purchased from common commercial sources and used as received. $RuCl_2(PPh_3)_3$ was purchased from Sigma-Aldrich. All solvents were dried by using standard procedure.[15] Solvent such as toluene were dried and distilled over Na/benzophenone. The preparation of catalyst was carried out under argon atmosphere with freshly distilled dry THF or dichloromethane. All catalytic reactions were carried out under argon atmosphere using dried glassware and standard syringe/septa techniques. DRX-400 Varian spectrometer and Bruker Avance III 600 and 400 spectrometers were used to record ^{1}H, ^{13}C NMR and $^{31}P\{^{1}H\}$ NMR. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane ; spin−spin coupling constant (J) are expressed in Hz, and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, and br s = broad singlet. IR spectra were recorded on Perkin Elmer Instrument at room temperature making KBr pellet. MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass Q-TOF LC/MS 6520. X-ray crystallographic data were collected using Agilent Super Nova (Single source at offset, Eos) diffractometer and Bruker Nonius SMART APEX CCD diffractometer equipped with a graphite monochromator. Data refinement and cell reduction were carried out by CrysAlisPro. Structures were solved by direct methods

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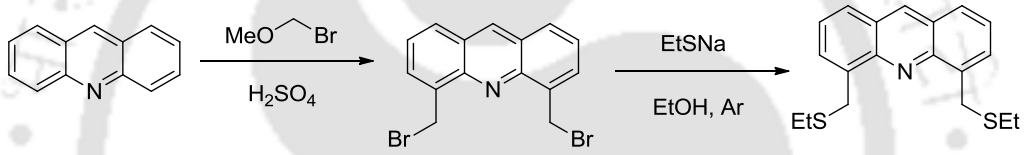
using SHELXS-97 and refined by full-matrix least-squares on F2 using SHELXL-97. All of the non-H atoms were refined anisotropically. SQUEEZE was used to reduce contribution of solvent molecule (diethylether/ acetonitrile) to the overall electron density. Column Chromatography was done with SRL Silica gel 100-200 mesh. Organic azides should be handled under proper safety precautions such as i) Chlorinated solvent should not be used as reaction media ii) organic azides should not be distilled iii) It should be kept in dark at low temperature.[16]

A. General experimental procedure for the synthesis of ligands and complexes:

1) Synthesis of ligands:

1.a) Synthesis of 4,5-bis(ethylthiomethyl)acridine (L_1):



Scheme 2.13: Synthesis of SNS ligand (L_1)

NaOH (0.47g, 12 mmol) was taken in 5 mL of water and the resulting NaOH solution was added dropwise to a solution of ethanethiol (0.62g, 10 mmol) in ethanol (50 mL). Then the resulting mixture was refluxed for 30 min and then 4,5-bis(bromomethyl)acridine (1.8 g, 5 mmol) in tetrahydrofuran (10 mL), was added to it. After that, the reaction mixture was refluxed for another 2 h. After cooling to room temperature, the reaction mixture was poured into distilled water (100 mL) and extracted with 80 mL of chloroform. The extract was washed with water (3 × 25 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure on a rotary evaporator and the crude mixture was purified by silica gel column chromatography using hexane: ethyl acetate (9.5:0.5) to afford the pure ligand as a yellow solid (Yield: 1.3 g, 80%. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.71 (s, 1H), 7.89 (dd, *J* = 8.5, 1.4 Hz, 2H), 7.76 (dd, *J* = 6.9, 1.3 Hz, 2H), 7.48 (dd, *J* = 8.4, 6.7 Hz, 2H), 4.60 (s, 4H), 2.60 (q, *J* = 7.4 Hz, 4H), 1.31 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (150 MHz,

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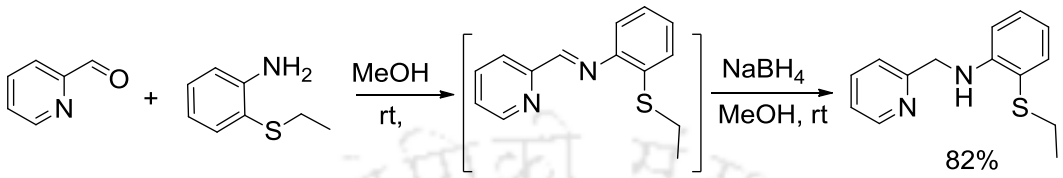
$CDCl_3$): δ (ppm) 146.5, 137.7, 136.4, 129.4, 127.3, 126.9, 125.5, 31.8, 26.5, 14.7. HRMS (ESI) calcd for $C_{19}H_{21}NS_2$ $[M + H]^+$ 328.1194, Found 328.1192.

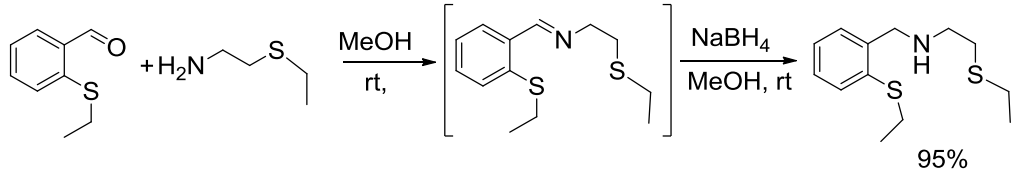
1.b) Synthesis of (2-(ethylthio)-N-(pyridin-2-ylmethyl)aniline (L_2):



Scheme 2.14: Synthesis of NNS ligand (L_2)

Pyridine-2-carboxaldehyde (0.721 g, 6.7 mmol) and 2-(ethylthio)aniline (1.0 g, 6.5 mmol) were dissolved in dry MeOH (25 mL) and the resulting mixture was refluxed for 24 h. After cooling the reaction, $NaBH_4$ (1.228 g, 32.5 mmol) was added portion wise in stirring condition at 0 °C and the stirring was continued for 6 hours at room temperature. Then the solvent was evaporated and 25 ml water was added and neutralized by acetic acid. After that, it was extracted by CH_2Cl_2 (40 mL×3) and the combined organic phase was dried over Na_2SO_4. Then, the solvent was evaporated to get the crude product, which was purified further by silica gel column chromatography using 10-30 % ethyl acetate in hexane. Brown liquid (Yield 1.308 g, 82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62-8.58 (m, 1H), 7.63 (td, *J* = 7.7, 1.8 Hz, 1H), 7.43 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.20-7.10 (m, 2H), 6.64 (td, *J* = 7.5, 1.3 Hz, 1H), 6.54 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.02 (brs, 1H), 4.54 (s, 2H), 2.79 (q, *J* = 7.4 Hz, 2H), 1.25 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.9, 149.4, 148.8, 136.8, 136.2, 130.0, 122.1, 121.2, 117.9, 117.1, 110.5, 49.4, 29.2, 15.0. HRMS (ESI) calcd for $C_{14}H_{16}N_2S$ $[M + H]^+$: 245.1112; found, 245.1119.

1.c) Synthesis of 2-(ethylthio)-*N*-(2-(ethylthio)benzyl)ethan-1-amine (L_3):



Scheme 2.15: Synthesis of SNS ligand (L_3)

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A solution of 2-(ethylthio)benzaldehyde (2.127g, 12.79 mmol) and 2-(ethylthio)ethan-1-amine compound (1.282 g, 12.18 mmol) in 45 mL dry MeOH was refluxed for overnight. Then, the reaction mixture was cooled to room temperature and $NaBH_4$ (1.154 g, 30.5 mmol) was added portion wise in stirring condition at 0 $^{\circ}$C and the stirring was continued for 6 hours at room temperature. Then the solvent was evaporated and 60 ml water was added and neutralized by acetic acid. The aqueous layer was then extracted with CH_2Cl_2 (80 mL×3) and the combined organic phase was dried over Na_2SO_4. Then the solvent was evaporated to get the crude product, which was purified further by silica gel column chromatography using 10-30% ethyl acetate in hexane. White solid. (Yield 2.958 g, 95%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7.7, 2.2 Hz, 1H), 7.45-7.42 (m, 1H), 7.36 (ddt, *J* = 9.3, 7.7, 1.5 Hz, 1H), 7.32-7.27 (m, 1H), 4.37 (s, 2H), 3.52-3.43 (m, 1H), 3.08 (t, *J* = 7.3 Hz, 2H), 3.03-2.93 (m, 4H), 2.48 (q, *J* = 7.4 Hz, 2H), 1.33 (td, *J* = 7.3, 1.5 Hz, 3H), 1.22 (td, *J* = 7.4, 0.9 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.0, 131.8, 131.1, 130.6, 130.2, 127.4, 48.4, 45.6, 29.0, 27.7, 25.8, 14.7, 14.3. HRMS (ESI) calcd for $C_{13}H_{22}NS_2$ $[M + H]^+$: 256.1194; found, 256.1197.

B. Synthesis and characterization of of complexes:

2.a) Synthesis of acridine derived (SNS) ruthenium pincer complex 2.1A: To a solution of 4,5-bis(ethylthiomethyl)acridine (0.235 g, 0.721 mmol) in dry CH_2Cl_2 (10 mL) was added a solution of $RuCl_2(PPh_3)_3$ (0.553g, 0.576 mmol) in dry CH_2Cl_2 (10 mL) and stirred 12 h at room temperature under argon. The solvent was evaporated and the brown solid was washed with diethyl ether several times and dried under vacuum, resulting in the pure complex as a brown solid (Yield 0.372 g, 85%). The single crystal was grown by slow diffusion of diethyl ether in the $CHCl_3/CH_3CN$ solution of the complex.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 9.02 (s, 1H), 8.10 (d, *J* = 8.04 Hz, 2H), 7.77 (t, *J* = 9 Hz, 6H), 7.72 (d, *J* = 6.24 Hz , 2H), 7.50 (t, *J* = 7.32 Hz , 3H), 7.35-7.29 (m, 8H), 5.69 (d, *J* = 13.02 Hz, 2H), 4.29 (d, *J* = 13.08 Hz, 2H), 1.53-1.47 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 6H), 0.60-0.54 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 149.7, 143.2, 134.9 (d, *J*

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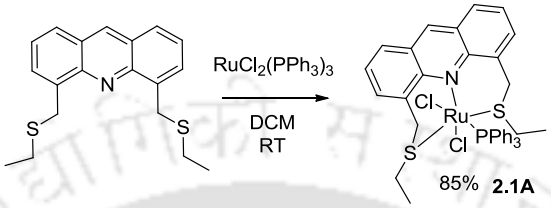
= 8.37 Hz), 134.6 (d, *J* = 46.48 Hz), 134.3, 130.8, 130.7, 129.3, 128.6, 127.2 (d, *J* = 9.36 Hz), 124.3, 35.5, 22.5, 12.4; $^{31}P\{^{1}H\}$ NMR (400 MHz, $CDCl_3$): δ (ppm) 54.84; Anal. Calc. for $C_{37}H_{36}Cl_2NPRuS_2$: C, 58.34; H, 4.76; N, 1.84 found C, 58.35; H, 4.71; N, 1.84; HRMS (ESI) calcd for $C_{37}H_{36}Cl_2NPRuS_2$ $[M - Cl]^+$: 726.0759; found, 726.0757.



Crystal data of complex 2.1A:

Formula	$C_{39}\ H_{39}\ Cl_2\ N_2\ P\ Ru\ S_2$
Mol. wt.	802.78
Crystal system	Triclinic
Space group	P -1
Temperature /K	296(2)
Wavelength /Å	0.71073
a /Å	9.7186(6)
b /Å	11.8743(7)
c /Å	18.0974(11)
α/°	71.496(4)
β/°	79.588(4)
γ/°	79.316(4)
V/ $Å^3$	1929.4(2)
Z	2
Density/Mgm^{-3}	1.382
Abs. Coeff. /mm^{-1}	0.724
Abs. correction	MULTI-SCAN

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F(000)	824
Total no. of reflections	18723
Reflections, I > 2σ(I)	4342
Max. 2θ/°	25.00
Ranges (h, k, l)	-11≤ h ≤11 -14≤ k ≤13 -21≤ l ≤ 20
Complete to 2θ (%)	98.9
Refinement method	Full-matrix least-squares on F^2
Goof (F^2)	1.033
R indices [I > 2σ(I)]	0.0633
R indices (all data)	0.0900

Selected bond lengths and angles:

Bond Distances [Å]	**Bond angles [°]**
Ru1 N1 12.561(5)	P1 Ru1 N1 170.02(12)
Ru1 P1 2.2587(16)	S1 Ru1 N1 89.53(12)
Ru1 S1 2.3394(16)	S2 Ru1 N1 90.43(12)
Ru1 S2 2.3210 (16)	Cl1 Ru1 N1 76.51(12)
Ru1 Cl1 2.3989(16)	Cl2 Ru1 N1 93.22(12)
Ru1 Cl2 2.4317(16)	Cl1 Ru1 Cl2 169.47(6)
	P1 Ru1 S1 92.60(6)

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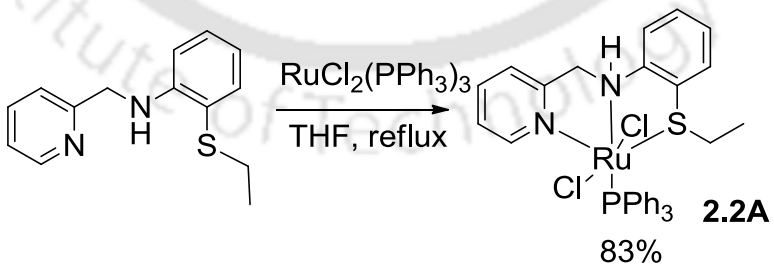
	S2 Ru1 S1	167.27(6)
	P1 Ru1 S2	89.63(6)
	P1 Ru1 Cl1	93.59(6)
	S2 Ru1 Cl1	98.06(6)
	S1 Ru1 Cl1	94.32(6)
	P1 Ru1 Cl2	96.72(6)
	S2 Ru1 Cl2	84.13(6)
	S1 Ru1 Cl2	83.16(6)

2.b) Synthesis of ruthenium pincer complex 2.2A: Ligand, 2-(ethylthio)-N-(pyridin-2-ylmethyl)aniline (0.030g, 0.13 mmol) was taken in 1 mL dry THF and was added dropwise to the solution of $[RuCl_2(PPh_3)_3]$ (0.107g, 0.11 mmol) in 4 mL degassed dry THF under argon. Then, it was refluxed for 6 hours. After cooling it down to the room temperature, 20 ml diethyl ether was added. The resulting precipitate was thoroughly washed with diethyl ether and dried under vacuum to get brown solid (Yield 0.046g, 83%). The single crystal was grown by slow diffusion of diethyl ether in the $CHCl_3$ solution of the complex.



^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.68 (d, *J* = 5.6 Hz, 1H), 7.70 (q, *J* = 8.4, 7.1 Hz, 6H), 7.61 – 7.56 (m, 2H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.43 – 7.30 (m, 12H), 6.91 (t, *J* = 6.6 Hz, 1H), 5.46 (t, *J* = 12.6 Hz, 1H), 5.17-5.13 (m, 1H), 2.71-2.66 (m, 1H), 2.41-2.36 (m,

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1H), 0.92 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 163.1, 157.2, 146.4, 140.1, 135.7 (d, *J*= 10.5 Hz), 135.4, 134.9 (d, *J* = 9.8 Hz), 133.7, 129.8, 129.2, 127.7 (d, *J* = 9.1 Hz), 127.6, 124.3, 123.5, 121.6, 57.0, 35.0, 13.5. $^{31}P\{^1H\}$ NMR (600 MHz, $CDCl_3$): δ (ppm) 50.15; Anal. Calc. for $C_{32}H_{31}Cl_2N_2PRuS$: C, 56.64; H, 4.60; N, 4.13 found C, 56.69; H, 4.60; N, 4.12; HRMS (ESI) calcd for $C_{32}H_{31}Cl_2N_2PRuS_2$ $[M - Cl]^+$: 643.0678; found, 643.0650.

Crystal data of complex 2.2A:

Empirical formula	C68 H72 Cl4 N4 O P2 Ru2 S2 C68
Formula weight	1431.30
Temperature, T	293 K
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a= 10.1370(4) Å α= 73.196(2)° b= 11.4066(4) Å β= 80.920(2)° c= 16.0632(6) Å γ= 67.294(2)°
Volume, *V* (Å^3)	1638.01(11)
Z	1
Density (calculated), Mg·m^{-3}	1.451
Absorption coefficient, *μ* (mm^{-1})	0.782
F(000)	734.0
Crystal size, mm^3	0.32 × 0.28 × 0.19
Theta range for data collection	0.997 to 24.75
Index ranges	-11 ≤ h ≤ 11, -12 ≤ k ≤ 13, -18 ≤ l ≤ 18
Reflections collected	4204

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Independent reflections	5581
Completeness to theta	0.997
Absorption correction	none
Max. and min. transmission	0.862 to 0.779
Refinement method	'SHELXL-97(Sheldrick, 1997)'
Data / restraints / parameters	5581 / 6/388
Goodness-of-fit on F^2	0.909
Final R indices [I>2sigma(I)]	R1 = 0.0473(3792), wR=0.1146(5581)
R indices (all data)	R1 = 0.0730, wR=0.0975
Extinction coefficient	0.782
Largest diff. peak and hole	1.089 and -0.549 e·$Å^{-3}$

Selected bond length and bond angle:

Bond lengths [Å]	**Bond angles [°]**
Ru1 N1 2.078(4)	N1 Ru1 N2 78.49(16)
Ru1 N2 2.124(4)	N1 Ru1 P1 98.45(13)
Ru1 P1 2.2967(14)	N2 Ru1 P1 176.93(12
Ru1 S1 2.3214(15)	N1 Ru1 S1 162.58(13)
Ru1 Cl2 2.3935(15)	N2 Ru1 S1 84.42(12)
Ru1 Cl1 2.4227(15)	P1 Ru1 S1 98.65(5)
	N1 Ru1 Cl2 85.61(12)
	N2 Ru1 Cl2 84.37(12)
	P1 Ru1 Cl2 95.20(5)

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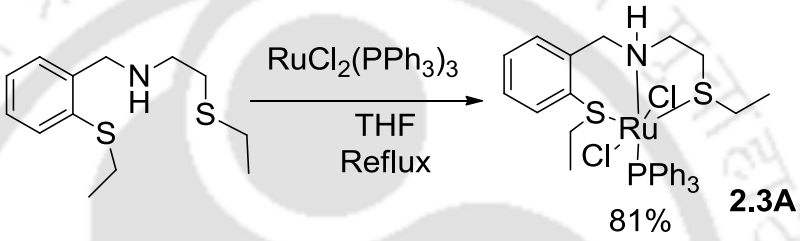
2.c) Synthesis of ruthenium pincer complex 2.3A: Ligand, 2-(ethylthio)-N-(2-(ethylthio)benzyl)ethan-1-amine (0.058 g, 0.22 mmol) was taken in 3 mL dry THF and was added dropwise to the solution of $[RuCl_2(PPh_3)_3]$ (0.181g, 0.18 mmol) in 5 mL degassed dry THF. Then, it was refluxed for 6 hours under argon atmosphere. After cooling it down to the room temperature, the solvent was evaporated to obtain the residue, which was thoroughly washed with diethyl ether and dried under vacuum to get yellow solid (Yield 0.103g, 81%). The single crystal was grown by slow diffusion of hexane in the $CHCl_3$ solution of the complex.



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1st dias. (Cis-isomer) (60%) 7.77-7.19 (m, 19H), 5.10 (t, *J* = 10.7 Hz, 1H), 3.94 (t, *J* = 11.8 Hz, 1H), 3.67-2.10 (m, 7H), 1.5-0.8 (m, 5H), 0.63 (t, *J* = 7.1 Hz, 3H). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2nd dias. (trans isomer) (40%) 7.77-7.19 (m, 19H), 4.89 (t, *J* = 10.8 Hz, 1H), 4.22 (t, *J* = 11.2 Hz, 1H), 3.67-2.10 (m, 7H), 1.5-0.8 (m, 5H), 0.69 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 1st+2nd dias. 140.7, 139.9, 136.9, 136.56, 136.3, 135.9, 135.9, 134.7, 134.7, 132.2, 131.0, 130.3, 130.1, 129.1, 128.7, 128.7, 127.5, 127.4, 127.4, 127.4, 55.0, 54.6, 51.9, 51.5, 35.6, 32.0, 31.0, 30.7, 30.0, 29.5, 26.0, 12.9, 12.9, 12.7. ^{31}P{^{1}H} NMR (600 MHz, $CDCl_3$): δ (ppm) 45.23 and 43.41. Anal. calc. for $C_{31}H_{36}Cl_2NPRuS_2$: C, 53.99; H, 5.26; N, 2.03 found C, 53.53; H, 5.38; N, 2.22; HRMS (ESI) calcd for $C_{31}H_{36}Cl_2NPRuS_2$ [M - Cl]$^+$: 654.0759; found, 654.0759.

Crystal data of complex 2.3A:

Empirical formula	C31 H36 Cl2 N P Ru S2
Formula weight	689.67
Temperature, T	293 K

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Crystal system	triclinic
Space group	P -1
Unit cell dimensions	a= 10.7565(6) Å α= 90.215(5) ° b= 12.0194(7) Å β= 92.041(5) ° c= 12.7360(8) Å γ=107.252(5) °
Volume, V ($Å^3$)	1571.34(16)
Z	2
Density (calculated), $Mg \cdot m^{-3}$	1.458
Absorption coefficient, μ (mm^{-1})	0.874
F(000)	708.0
Crystal size, mm^3	0.34 × 0.30 × 0.27
Theta range for data collection	0.998 to 25.00
Index ranges	$-10 \leq h \leq 12$, $-14 \leq k \leq 14$, $-15 \leq l \leq 13$
Reflections collected	3007
Independent reflections	5525
Completeness to theta	0.998
Absorption correction	multi-scan
Max. and min. transmission	0.792 to 1.000
Refinement method	'SHELXL-97(Sheldrick, 1997)'
Data / restraints / parameters	5525 / 0/345
Goodness-of-fit on F^2	0.977
Final R indices [I>2sigma(I)]	R1 = 0.0492(4271), wR=0.1385(5525)
R indices (all data)	R1 = 0.0705, wR=0.1196
Extinction coefficient	0.874
Largest diff. peak and hole	1.098and -0.566 $e \cdot Å^{-3}$

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Selected bond length and bond angle:

Bond lengths [Å]	**Bond angles [°]**
Ru1 N1 2.179(4)	N1 Ru1 P1 175.43(10)
Ru1 P1 2.3110(14)	N1 Ru1 S2 84.13(10)
Ru1 S2 2.3506(13)	P1 Ru1 S2 91.32(5)
Ru1 S1 2.3646(13)	N1 Ru1 S1 90.08(10)
Ru1 Cl1 2.4107(13)	P1 Ru1 S1 94.41(5)
Ru1 Cl2 2.4299(13)	S2 Ru1 S1 171.28(5)
	N1 Ru1 Cl1 86.79(11)
	P1 Ru1 Cl1 93.86(5)
	S2 Ru1 Cl1 93.84(5)

3) Representative procedure for the catalytic aza-Wittig type reaction of alcohol and azide.

In a two necked round bottom flask, equipped with a condenser, complex **2.1A** (0.01 mmol), KOH (0.05 mmol) and dry toluene (3 ml) were added under argon atmosphere. To this suspension alcohol (1 mmol), azide (1 mmol) and PPh_3 (1 mmol) in dry toluene (2 ml) were subsequently added under argon atmosphere. The solution was refluxed to 135 $^{\circ}$C (bath temperature) with stirring under argon atmosphere for the specified time. Then the reaction mixture was allowed to cool to the room temperature and was filtered through celite. After that, the solvent was removed and 1,4-dioxane or acetonitrile was added as internal standard to the reaction mixture and take ^{1}H NMR in $CDCl_3$ to get the NMR yield. Purification was done by column chromatography over silica gel using 0.5:10 mixture of ethyl acetate-hexane containing 2% triethylamine as eluent to afforded pure imine product. Characterization data of the products are given below.

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4) Representative procedure for the catalytic Wittig type reaction of alcohol and phosphonium salt.

In a two-necked round bottom flask, equipped with a condenser, complex **2.1A** (0.01 mmol), alcohol (1 mmol), phosphonium salt (1.2 mmol), ^{t}BuOK (1.3 mmol) and dry dioxane (5 ml) were added under argon atmosphere. The solution was then refluxed to 135 $^{\circ}$C (bath temperature) with stirring under argon for the specified time. Then the reaction mixture was allowed to cool to the room temperature and was filtered through celite and the solvent was removed. The crude product was analyzed by ^{1}H NMR to determine the E/Z. Purification was done by column chromatography over silica gel using hexane or 0.5:10 mixture of ethyl acetate-hexane as eluent to afforded pure alkene product.

5) Synthesis of (S)-1,2,3,10,11,11a-hexahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-5-one (2.13). In a two- necked round bottom flask, the complex **2.1A** (0.005 mmol), (S)-(2-azidophenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone (0.5 mmol) (**2.8**), PPh_3 (0.5 mmol), KOH (5 mol%) and dry toluene (5 ml) were placed under Argon atmosphere. The mixture was stirred at 135 $^{\circ}$C for 18 h under argon atmosphere. After that, the reaction mixture was cooled to room temperature and filtered through celite. Then the solvent was removed under reduced pressure and the crude reaction mixture was purified by column chromatography (silica gel; 75% ethyl acetate and hexane).

6) (S)-1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-5-one (2.14). In a two-necked round bottom flask, the complex **2.1A** (0.005 mmol), (S)-(2-azidophenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone (0.5 mmol) (**2.8**), PPh_3 (0.5 mmol), KOH (5 mol%), diphenylacetylene (0.75 mmol) and dry toluene (5 ml) were placed under argon atmosphere. The mixture was stirred at 135 $^{\circ}$C for 18 h under argon atmosphere. After the reaction finished, the reaction mixture was cooled to room temperature and filtered through celite. Then the solvent was removed under reduced pressure and the crude reaction mixture was purified by column chromatography (silica gel; 75% ethyl acetate and hexane).

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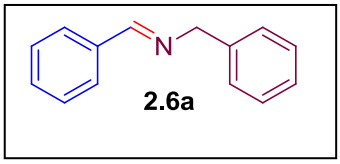
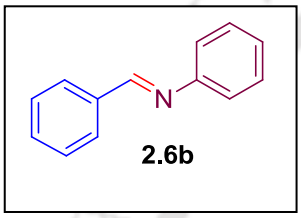
2.5. Characterization data of products:

N-Benzylidene-1-phenylmethanamine (2.6a).[17]



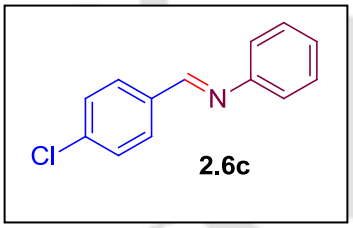
Pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.43 (s, 1H), 7.83-7.81 (m, 2H), 7.46-7.45 (m, 3H), 7.38-7.37 (m, 4H), 7.31-7.27 (m, 1H), 4.83 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 162.1, 139.4, 136.3, 130.9, 128.7, 128.6, 128.4, 128.1, 127.1, 65.2.

N-Benzylideneaniline (2.6b).[18]



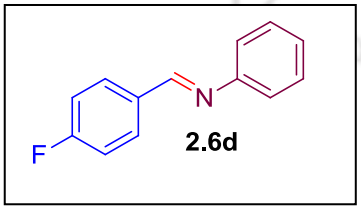
Pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.49 (s, 1H), 7.95-7.94 (m, 2H), 7.52- 7.51 (m, 3H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.29-7.24 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 160.6, 152.2, 136.3, 131.5, 129.3, 128.9, 128.9, 126.1, 121.0.

N-(4-Chlorobenzylidene)aniline (2.6c).[18]



Pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.34 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.34-7.31 (m, 2H), 7.18-7.13 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 159.0, 151.8, 137.5, 134.8, 130.1, 129.3, 129.2, 126.3, 121.0.

N-(4-Fluorobenzylidene)aniline (2.6d).[19]



Pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.33 (s, 1H), 7.83-7.81 (m, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.17-7.14 (m, 1H), 7.12 (dd, *J* = 7.3 Hz, 1.1 Hz, 2H), 7.08 (t, *J* = 8.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 164.82(d, *J* = 250 Hz), 158.9, 151.97, 132.7 (d, *J* = 3.03 Hz), 130.9 (d, *J* = 8.74 Hz), 129.3, 126.1, 120.9, 116.1 (d, *J* = 21.85 Hz).

N-(4-Methoxybenzylidene)aniline (6e).[17]

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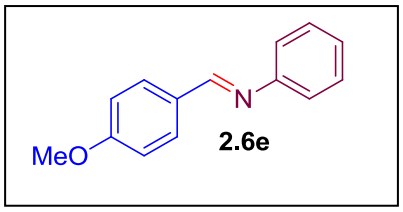
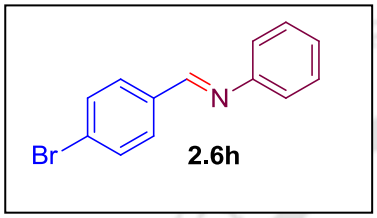


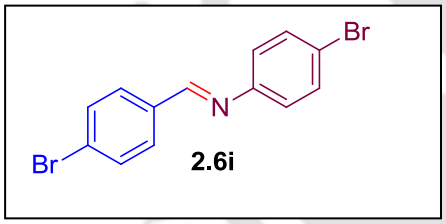
Pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.42 (s, 1H), 7.90 (d, *J* = 8.7 Hz, 2H), 7.43 (t, *J* = 8.3 Hz, 2H), 7.26-7.25 (m, 3H), 7.02 (d, *J* = 8.8 Hz) 2H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 162.3, 159.7, 152.4, 130.6, 129.3, 129.2, 125.6, 120.9, 114.2, 55.5.

N-(4-Bromobenzylidene)aniline (2.6h).[18]



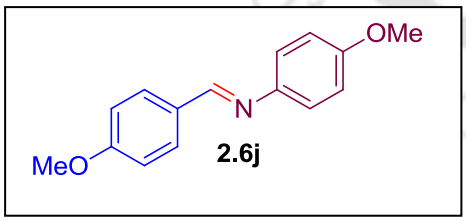
Pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.42- 7.38 (m, 2H), 7.22-7.20 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 159.0, 151.8, 137.5, 134.8, 130.1, 129.3, 129.2, 126.3, 121.0.

4-Bromo-N-[(4-bromophenyl)methylene]benzenamine (2.6i).[20]



Pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.38 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 159.5, 150.7, 134.9, 132.4, 132.2, 130.3, 126.3, 122.7, 119.8.

4-Methoxy-N-[(4-methoxyphenyl)methylene]benzenamine (2.6j).[18]



Pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.41 (s, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 162.1, 158.1, 158.0, 145.3, 130.3, 129.5, 122.2, 114.4, 114.2, 55.6, 55.5.

N-(2-Naphthalenylmethylene)benzenemethanamine (2.6k).[21]

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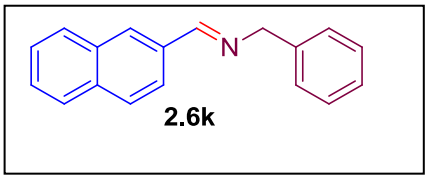
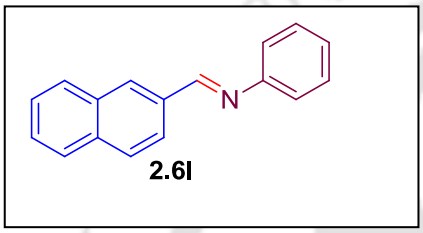


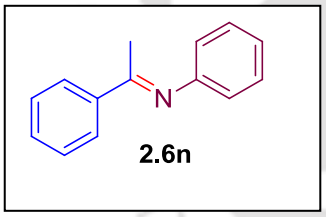
White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.53 (s, 1H), 8.07- 8.04 (m, 2H), 7.90-7.83 (m, 3H), 7.52-7.50 (m, 2H), 7.39-7.24 (m, 5H), 4.88 (s, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 162.2, 139.4, 134.9, 134.0, 133.2, 130.2, 128.7, 128.6, 128.6, 128.2, 128.0, 127.3, 127.1, 126.6, 124.1, 65.3.

N-(2-Naphthalenylmethylene)benzenamine (2.6l).[18]



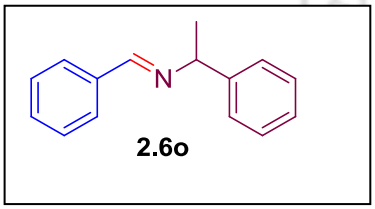
White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.62 (s, 1H), 8.20 -8.16 (m, 2H), 7.95- 7.87 (m, 3H), 7.56 -7.53 (m, 2H), 7.44 -7.40 (m, 2H), 7.28-7.25 (m, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 160.5, 152.2, 135.2, 134.1, 133.2, 131.4, 129.3, 128.9, 128.8, 128.1, 127.7, 126.7, 126.1, 124.1, 121.1.

N-(1-Phenylethylidene)benzenamine (2.6n).[22]



White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.97 (d, *J* = 8.1 Hz, 2H), 7.47- 7.44 (m, 3H), 7.35 (t, *J* = 8.1 Hz, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 165.6, 151.83, 139.6, 130.6, 129.1, 128.5, 127.3, 123.3, 119.5, 17.5.

N-Benzylidene-α-methylbenzylamine (2.6o).[23]



Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.36 (s, 1H), 7.78-7.76 (m, 2H), 7.43-7.42 (m, 2H), 7.39-7.38 (m, 3H), 7.33 (t, *J* = 5.1 Hz, 2H), 7.23 (t, *J* = 4.8 Hz, 1H), 4.53 (q, *J* = 6.6 Hz, 1H), 1.59 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): 159.6, 145.2, 136.5, 130.7, 128.6, 128.5, 128.4, 126.9, 126.7, 69.8, 24.9.

N-[(2-Aminophenyl)methylene]benzenamine (2.6p).[24]

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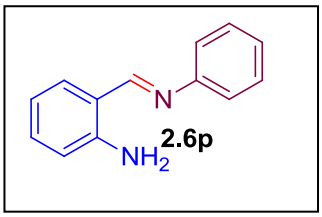
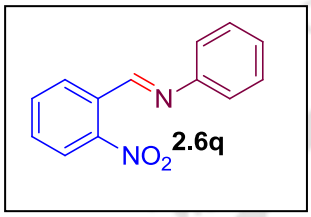


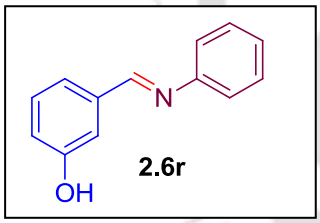
Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.46 (s, 1H), 7.34-7.25 (m, 3H), 7.16- 7.11 (m, 4H), 6.66 (t, *J* = 7.88 Hz, 2H); 6.46 (brs, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 163.3, 152.1, 148.9, 134.5, 131.96, 129.3, 125.7, 121.1, 117.8, 116.4, 115.9. HRMS (ESI) calcd for $C_{14}H_{13}N_2$ $[M + H]^+$: 197.1079; found, 197.1073.

N-[(2-Nitrophenyl)methylene]benzenamine (2.6q).[25]



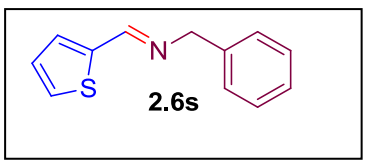
White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.95 (s, 1H), 8.32 (d, *J* = 7.8 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H) 7.75 (t, *J* = 8.2 Hz, 1H), 7.64- 7.60 (m, 1H), 7.43 (t, *J* = 7.92 Hz, 2H), 7.30- 7.26 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 156.0, 151.2, 149.4, 133.7, 131.3, 130.3, 129.9, 129.4, 127.1, 124.7, 121.3.

3-Hydroxybenzalaniline (2.6r).[26]



White solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.37 (s, 1H), 7.46 (s, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 6.6 Hz, 1H), 7.23 (d, *J* = 7.4 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 161.5, 156.6, 151.4, 137.1, 130.2, 129.4, 126.4, 122.3, 121.1, 119.5, 114.5. HRMS (ESI) calcd for $C_{13}H_{11}NO$ $[M + H]^+$: 198.0919; found, 198.0911.

N-(2-Thienylmethylene)benzenemethanamine (2.6s).[18]



Pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.50 (s, 1H), 7.45-7.37 (m, 6H), 7.35-7.32 (m, 1H), 7.12 (t, *J* = 6.6 Hz, 1H), 4.85 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): 155.2, 142.4, 139.1, 130.7, 129.0, 128.5, 128.0, 127.4, 127.0, 64.4.

N-(2-Pyridinylmethylene)benzenemethanamine (2.6t).[27]

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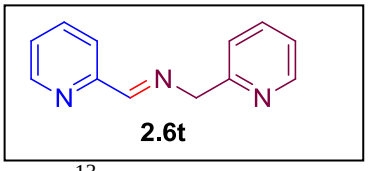
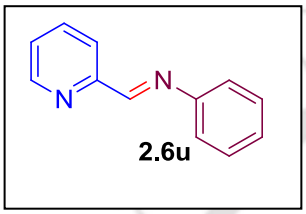


2.6t

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.66 (d, *J* = 6 Hz, 1H), 8.56 (s, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.75-7.62 (m, 2H), 7.42-7.33 (m, 2H), 7.18 (m, 1H), 5.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 164.1, 158.8, 154.5, 149.6, 149.5, 136.8, 136.7, 125.1, 122.5, 122,3, 121.6, 66.7.

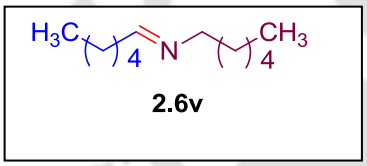
N-(2-Pyridinylmethylene)benzenamine (2.6u).[28]



2.6u

Light Yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.64 (d, *J* = 6.5 Hz, 1H), 8.53 (s, 1H), 8.13 (d, *J* = 11.8 Hz, 1H), 7.74 (t, *J* = 11.5 Hz, 1H), 7.36-7.28 (m, 3H), 7.23-7.19 (m, 3H) ; ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 160.7, 154.7, 151.1, 149.8, 136.8, 129.3, 126.8, 125.3, 122.0, 121.2.

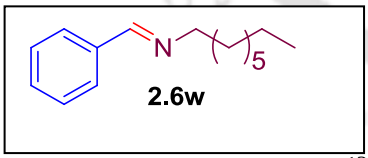
N-Hexyllidenehexane-1-amine (2.6v).[17]



2.6v

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.59 (s, 1H), 3.31 (t, *J* = 6.9 Hz, 3H), 2.20-2.18 (m, 2H), 1.56-1.51 (m, 2H), 1.50-1.46 (m, 2H), 1.30-1.25 (m, 10H), 0.88-0.84 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 165.0, 61.5, 35.9, 31.7, 31.6, 30.8, 27.0, 25.9, 22.7, 22.6, 14.1, 14.1.

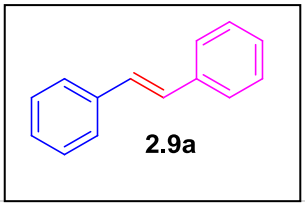
N-octyl-1-phenylmethanimine (2.6w).[29]



2.6w

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.27 (s, 1H), 7.73-7.71 (m, 2H), 7.41-7.39 (m, 3H), 3.60 (t, *J* = 8.0 Hz, 2H), 1.71-1.68 (m, 2H), 1.33-1.27(m, 10H), 0.88 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 160.8, 130.5, 128.7, 128.1, 62.0, 32.0, 31.0, 29.6, 29.4, 27.5, 22.8, 14.2.

E-Stilbene (2.9a).[30]


2.9a

White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.58-7.56 (m, 4H), 7.44-7.40 (m, 4H), 7.34-7.31 (m, 2H), 7.17 (s, 2H).

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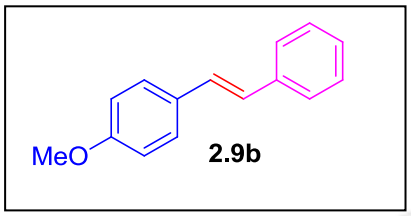
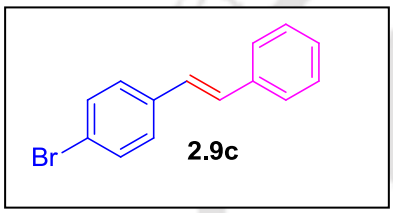
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 137.5, 128.8, 128.8, 127.7, 126.6.

E-1-Methoxy-4-styryl-benzene (2.9b).[30]



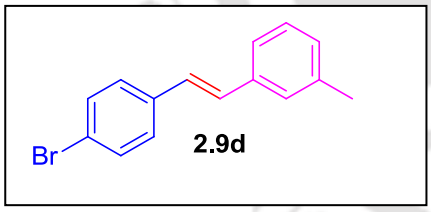
White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41 (d, *J* = 5.1 Hz, 2H), 7.38 (d, *J* = 5.3 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.17-7.15 (m, 1H), 6.99 (d, *J* = 16.3 Hz, 1H), 6.90 (d, *J* = 16.3 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 159.4, 137.7, 130.2, 128.8, 128.3, 127.8, 127.3, 126.7, 126.4, 114.2, 55.5.

E-1-Bromo-4-styryl-benzene (9c).[31]



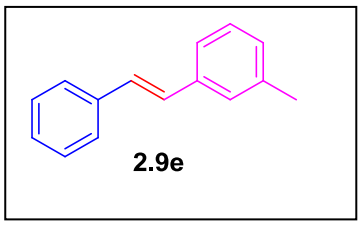
White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.44-7.40 (m, 4H), 7.31-7.2 (m, 4H), 7.22-7.18 (m, 1H), 7.02 (d, *J* = 16.2 Hz, 1H), 6.95 (d, *J* = 16.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 137.1, 136.5, 131.9, 129.6, 128.9, 128.1, 128.0, 127.6, 126.7, 121.4.

E-1-(4-Bromostyryl)-3-methylbenzene (2.9d).[32]



White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.39 (d, *J*= 7.5 Hz, 2H), 7.30-7.17 (m, 5H), 7.03-7.01 (m, 1H), 6.99 (d, *J* = 16.0 Hz, 1H), 6.93 (d, *J* = 16.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 138.5, 137.1, 136.6, 131.9, 129.7, 128.9, 128.8, 128.1, 127.4, 127.3, 123.9, 121.4, 21.6.

E-1-Methyl-3-styryl-benzene (2.9e).[33]



White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.48 (d, *J* = 7.3 Hz, 2H), 7.34-7.28 (m, 4H), 7.24-7.20 (m, 2H), 7.06-7.04 (m, 3H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 138.3, 137.6, 137.4, 129.0, 128.8, 128.7, 128.6, 128.6, 127.7, 127.3, 126.6, 123.86, 21.5.

(E)-1-Methyl-3-(4-methylstyryl)benzene (2.9f).[34]

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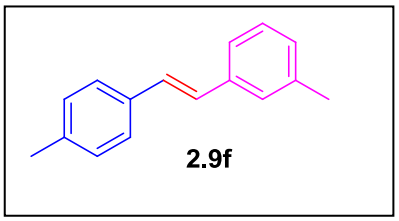
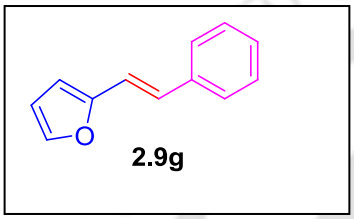


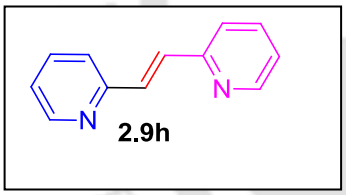
White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42 (d, *J* = 7.96 Hz, 2H), 7.32 (d, *J* = 9.8 Hz, 2H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 2H), 7.12-7.02 (m, 3H), 2.38 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 138.3, 137.6, 137.6, 134.8, 129.3, 128.7, 128.6, 128.4, 128.0, 127.2, 126.5, 123.7, 21.6, 21.4.

E-2-Styryl-furan (2.9g).[30]



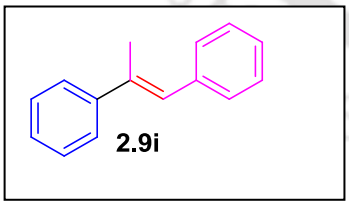
White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45-7.19 (m, 6H), 7.00 (d, *J* = 16.2 Hz, 1H), 6.85 (d, *J* = 16.3 Hz, 1H), 6.39-6.38 (m, 1H), 6.31 (d, *J* = 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 153.4, 142.3, 137.2, 128.8, 127.7, 127.3, 126.5, 116.7, 111.8, 108.7.

E-1,2-Bis(2-pyridyl)ethylene (2.9h).[35]



Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.55 (d, *J* = 5.6 Hz, 2H), 7.62-7.57 (m, 4H), 7.38-7.35 (m, 2H), 7.12-7.09 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 155.1, 149.8, 136.7, 131.9, 123.4, 122.7.

(E/Z)-1,2-Diphenylprop-1-ene (2.9i).[36]



White solid. 7.52 (d, *J* = 7.88 Hz, 2H), 7.40-7.36 (m, 6H), 7.31-7.25 (m, 2H), 6.84 (s, 1H, E-isomer), 6.48 (s, 1H, Z-isomer), 2.29 (s, 3H, E-isomer), 2.21 (s, 3H, Z-isomer). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) (E) 144.1, 138.5, 137.6, 129.3, 128.6, 128.5, 128.0, 127.9, 126.6, 126.1, 17.6. (Z) 142.3, 138.9, 137.8, 129.1, 128.6, 128.0, 127.0, 126.7, 126.7, 126.2, 27.2.

Z-1-Penten-1-ylbenzene (2.9j).[37]

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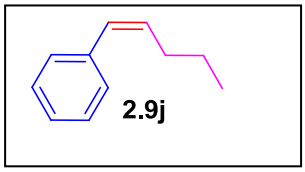
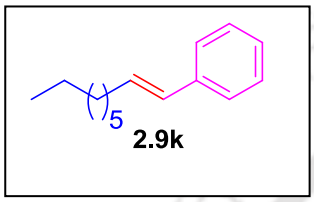


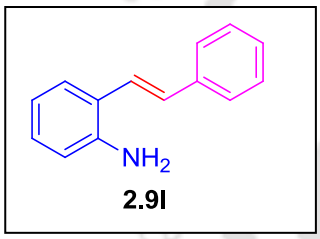
Colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.27-7.19 (m, 4H), 7.14-7.08 (m, 1H), 6.35-6.28 (m, 1H), 6.18-5.55 (m, 1H), 2.24-2.20 (m, 2H), 1.43-1.39 (m, 2H), 0.87-0.84 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 138.0, 133.2, 129.0, 128.9, 128.2, 126.5, 30.8, 23.3, 14.0.

E-Non-1-en-1-ylbenzene (2.9k).[5]



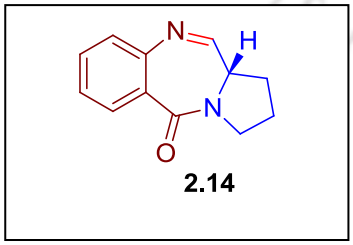
Colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42-7.33 (m, 4H), 7.27-7.23 (m, 1H), 6.45 (d, *J* = 15.8 Hz, 1H), 6.33-6.28 (m, 1H), 2.27 (td, J = 7.9, 1.1 Hz, 1H), 1.41-1.33 (m, 10H), 0.96 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 138.1, 131.4, 129.8, 128.6, 126.8, 126.0, 33.2, 32.0, 29.8, 29.5, 29.3, 22.8, 14.2.

E-2-Styrylaniline (2.9l). [38]



White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54 (d, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.31-7.27 (m, 1H), 7.20 (d, J = 16.1 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 7.02 (d, *J* = 16.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 144.1, 137.7, 130.5, 128.8, 127.7, 127.4, 126.6, 124.5, 124.2, 119.3, 116.4.

(S)-1,2,3,11a-Tetrahydro-5H-pyrrolo[1,2-a][1,4]benzodiazepin-5-one (2.14).[39]



White solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.04 (d, *J* = 7.7 Hz, 1H), 7.78 (d, *J* = 4.5 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.33 (t, *J* = 8.6 Hz, 2H), 3.89-3.83 (m, 1H), 3.76-3.72 (m, 1H), 3.60-3.53 (m, 1H), 2.35-2.30 (m, 2H), 2.10-2.04 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 165.1, 164.6, 145.8, 131.5, 130.4, 127.7, 126.9, 126.7, 53.6, 47.0, 29.7, 24.3. $[\alpha]_d^{24.6}$ +354 (c 0.02, $CHCl_3$); HRMS (ESI) calcd for $C_{12}H_{12}N_2O$ $[M + H]^+$: 201.1028; found, 201.1033.

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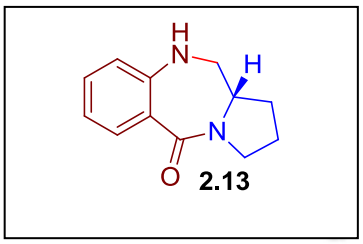
(S)-1,2,3,10,11,11a-Hexahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-5-one (2.13).[40]



2.13

Yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.94 (d, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 6.72 (t, *J* = 7.6 Hz, 1H), 6.51 (d, *J* = 8.1 Hz, 1H), 3.85-3.81 (m, 1H), 3.78-3.74 (m, 1H), 3.64-3.60 (m, 1H), 3.49 (m, 1H), 3.29-3.26 (m, 1H), 2.21- 2.15 (m, 1H), 1.88-1.86 (m, 1H), 1.82-1.77 (m, 1H), 1.67-1.62 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 166.8, 145.4, 133.0, 131.9, 119.2, 118.0, 118.0, 57.0, 53.2, 48.2, 30.7, 22.9. $[\alpha]_d^{19.2}$ +368 (c 0.02, $CHCl_3$); HRMS (ESI) calcd for $C_{12}H_{14}N_2O$ $[M + H]^+$: 203.1184; found, 203.1184.

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2.7: ^{1}H and ^{13}C NMR spectra of the compounds:

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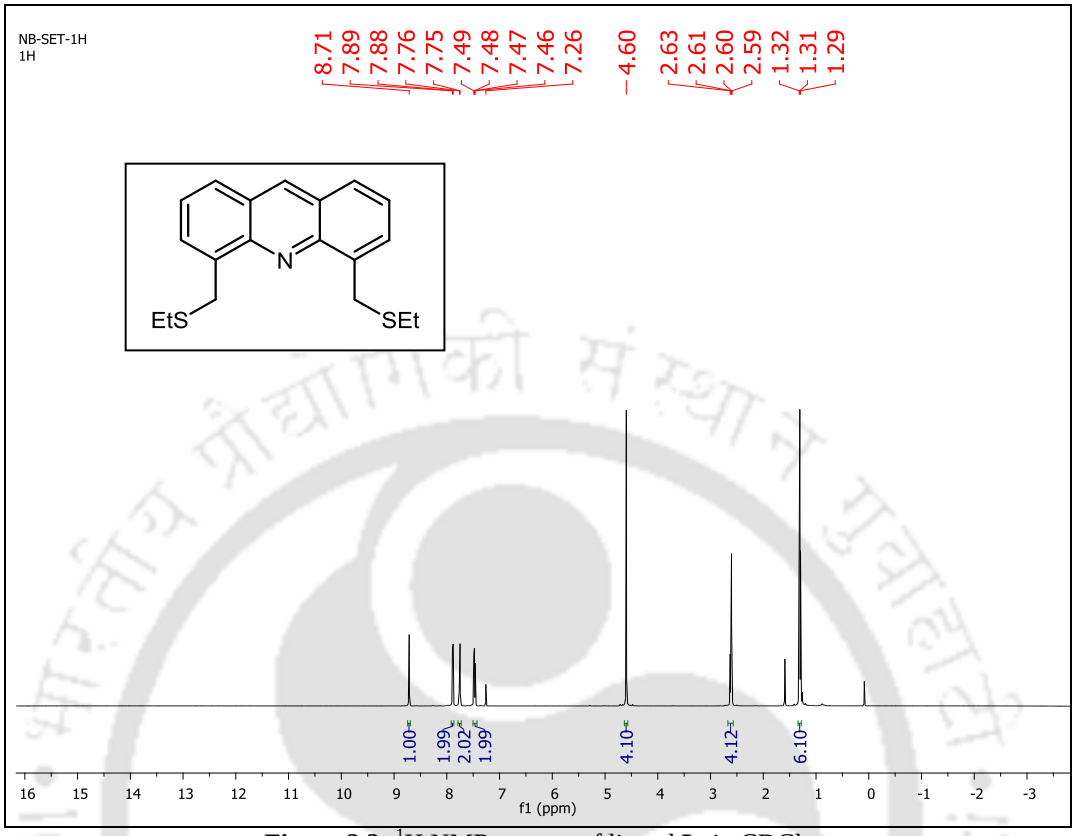

Figure 2.3: ^{1}H NMR spectra of ligand $\mathbf{L_1}$ in $CDCl_3$

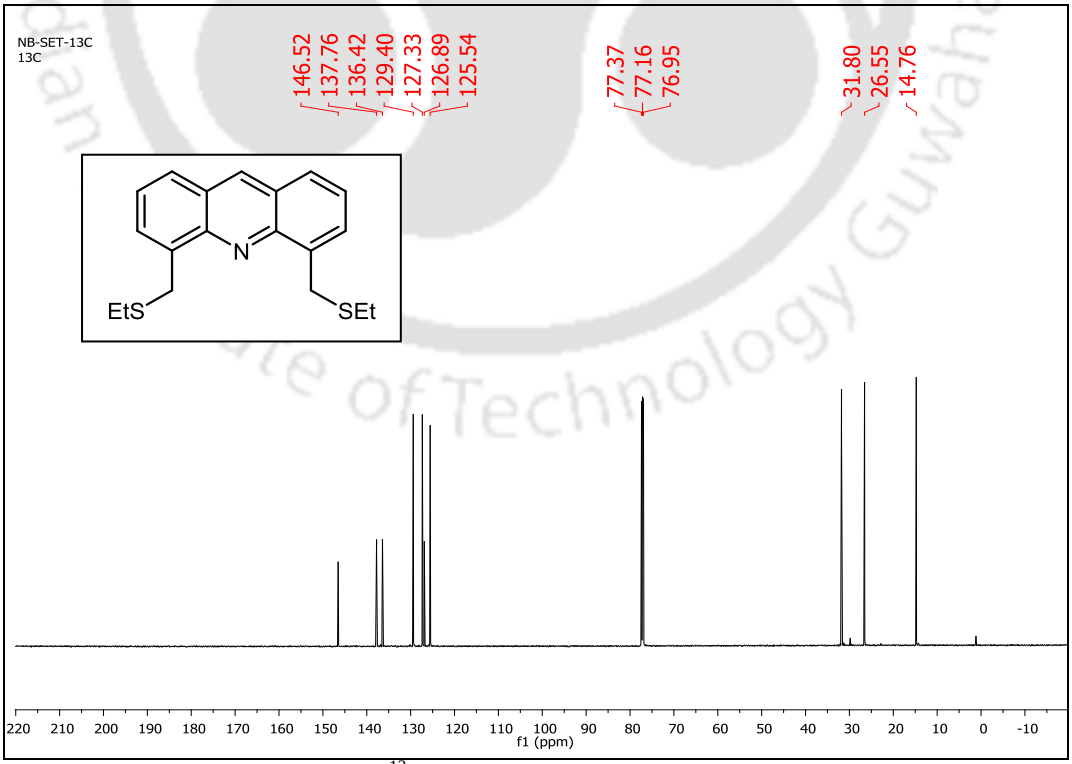

Figure 2.4: ^{13}C NMR spectra of ligand $\mathbf{L_1}$ in $CDCl_3$

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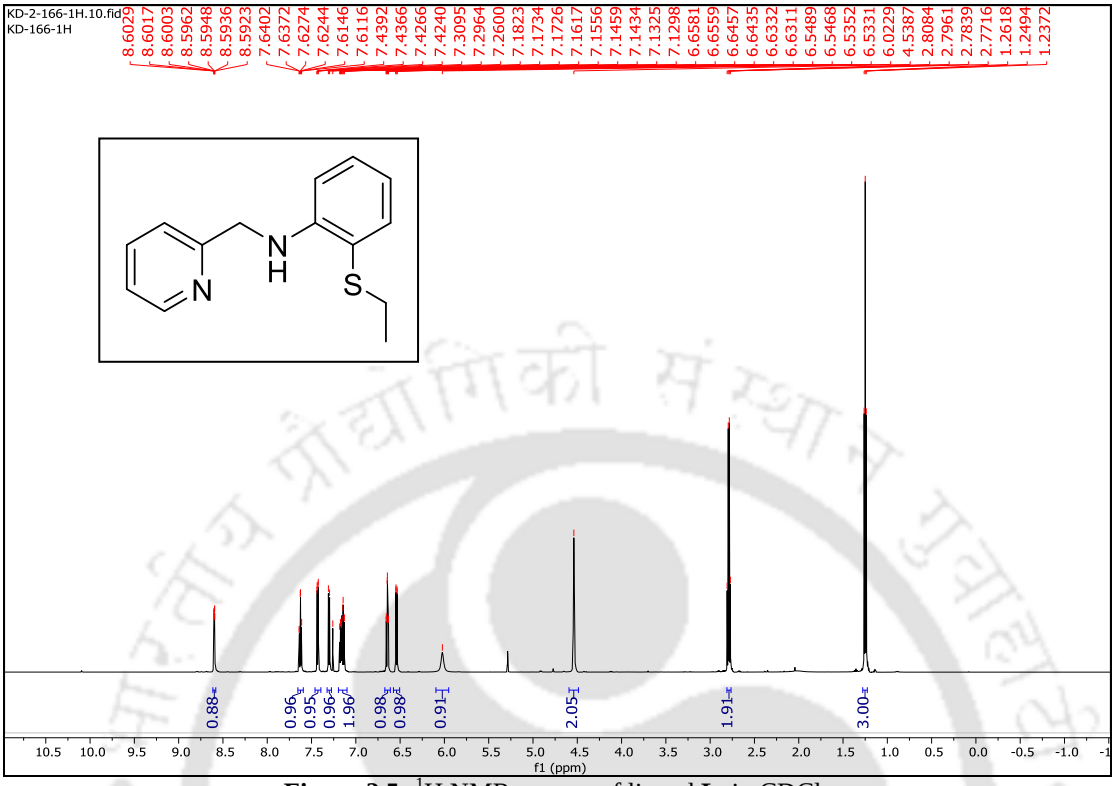

Figure 2.5: ^{1}H NMR spectra of ligand $\mathbf{L_2}$ in $CDCl_3$

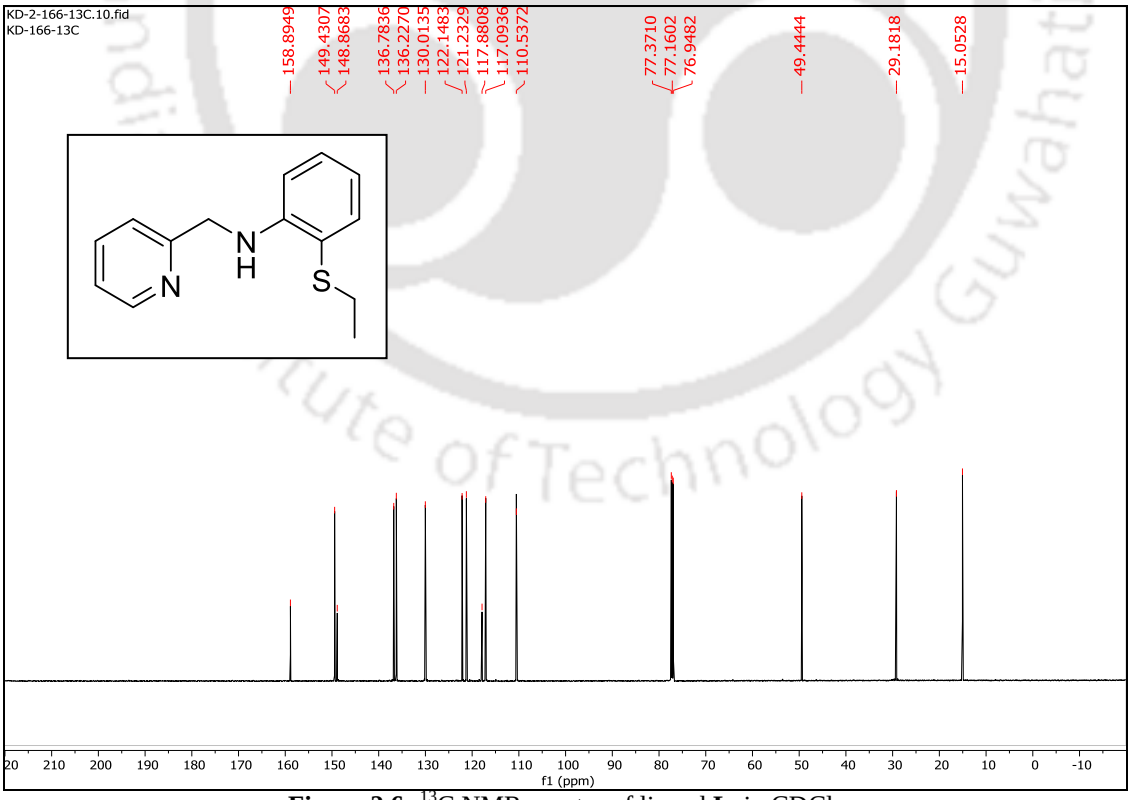

Figure 2.6: ^{13}C NMR spectra of ligand $\mathbf{L_2}$ in $CDCl_3$

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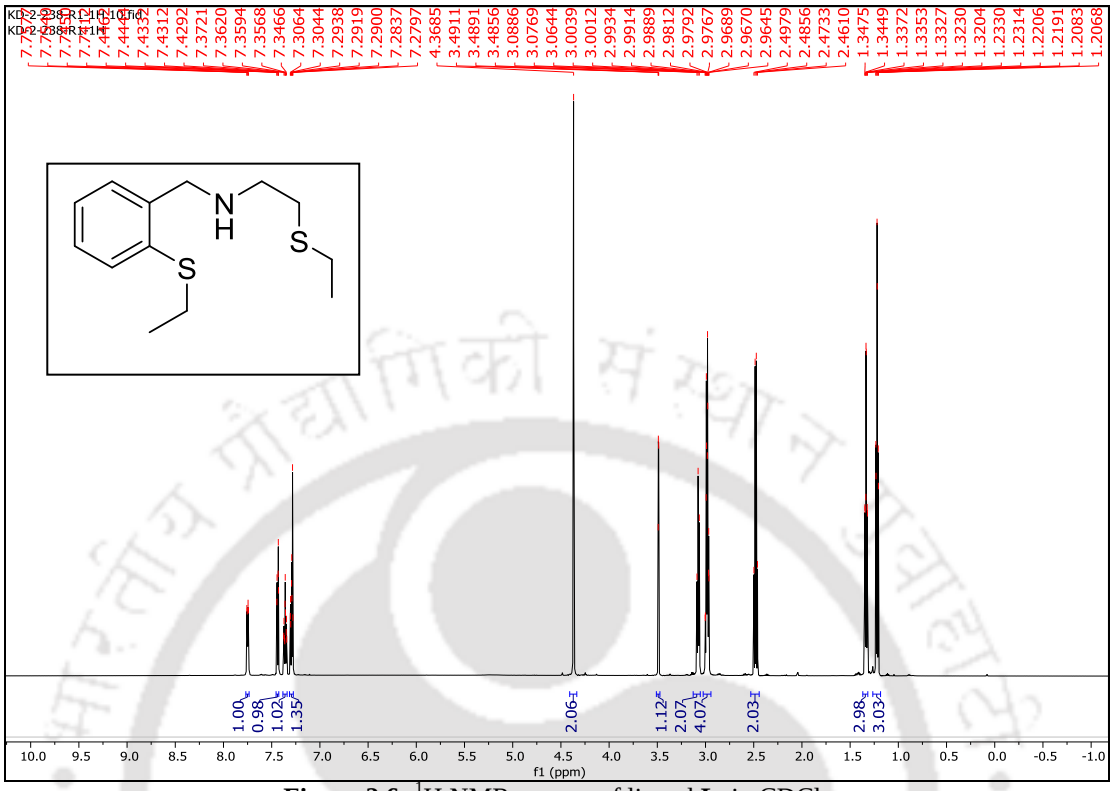

Figure 2.6: ^{1}H NMR spectra of ligand **L$_3$** in $CDCl_3$

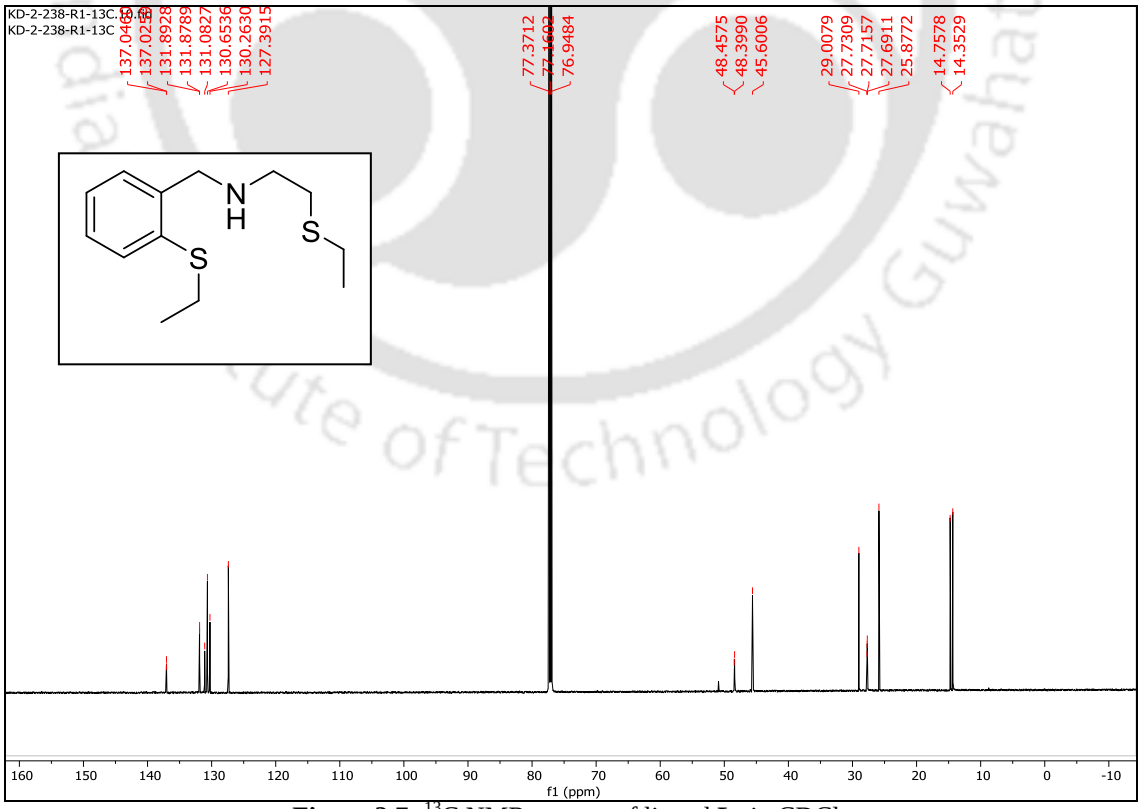

Figure 2.7: ^{13}C NMR spectra of ligand **L$_3$** in $CDCl_3$

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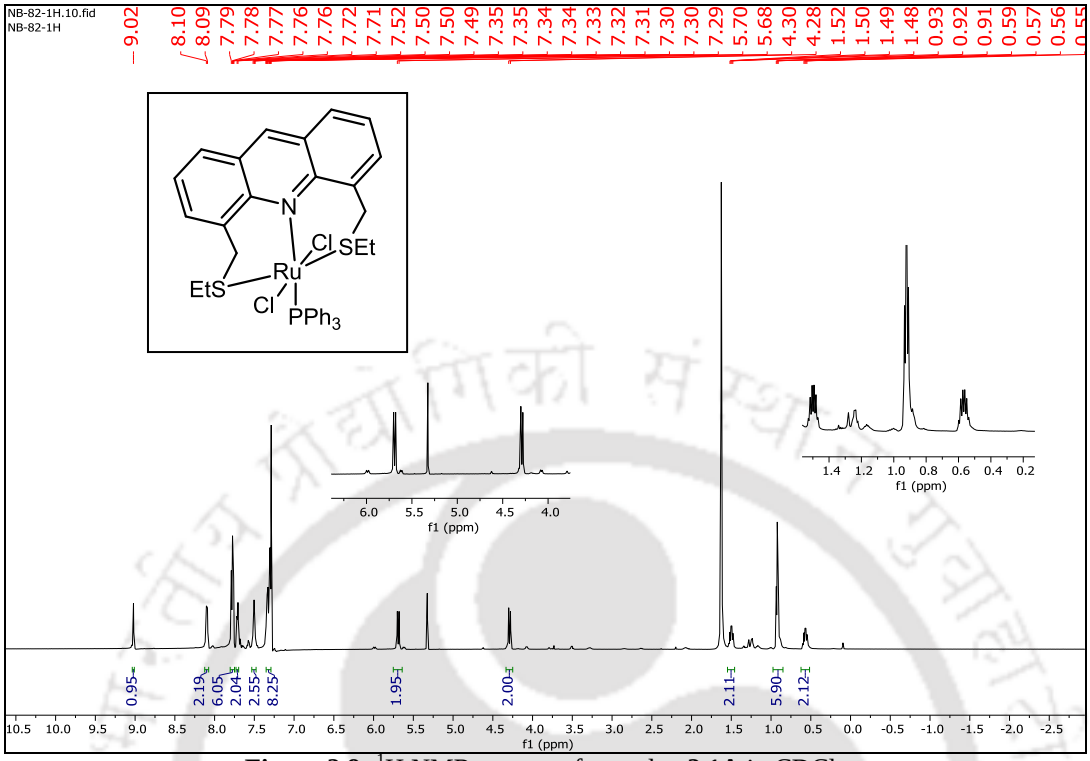

Figure 2.8: ^{1}H NMR spectra of complex **2.1A** in $CDCl_3$

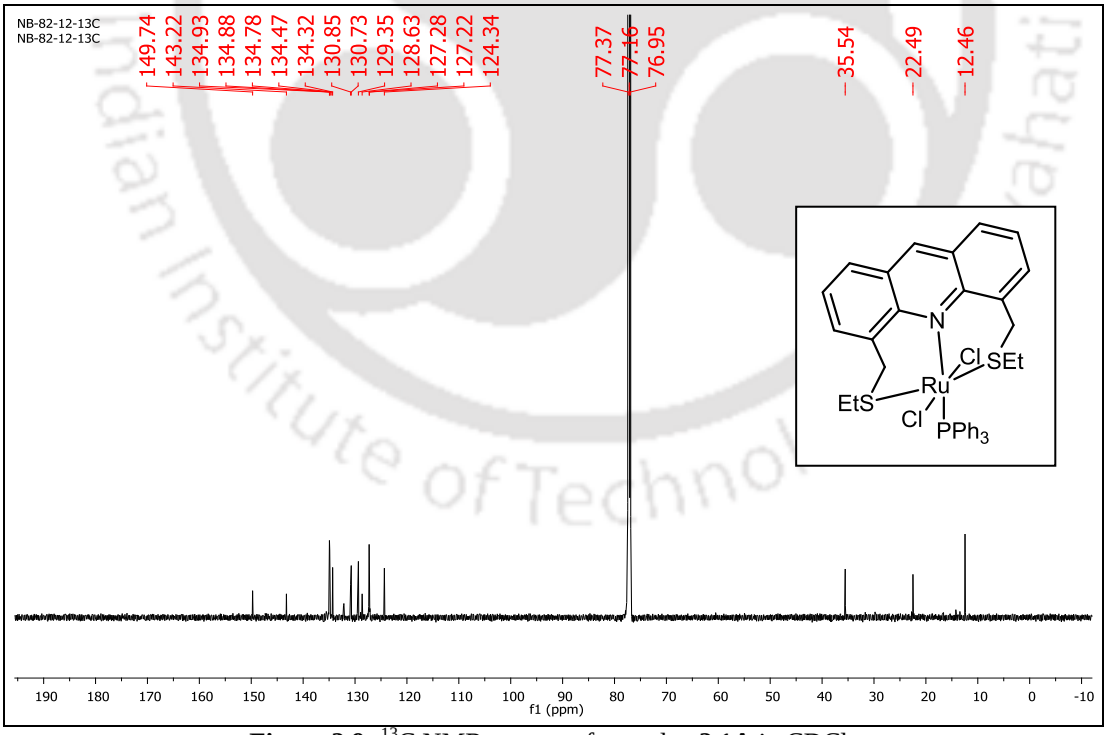

Figure 2.9: ^{13}C NMR spectra of complex **2.1A** in $CDCl_3$

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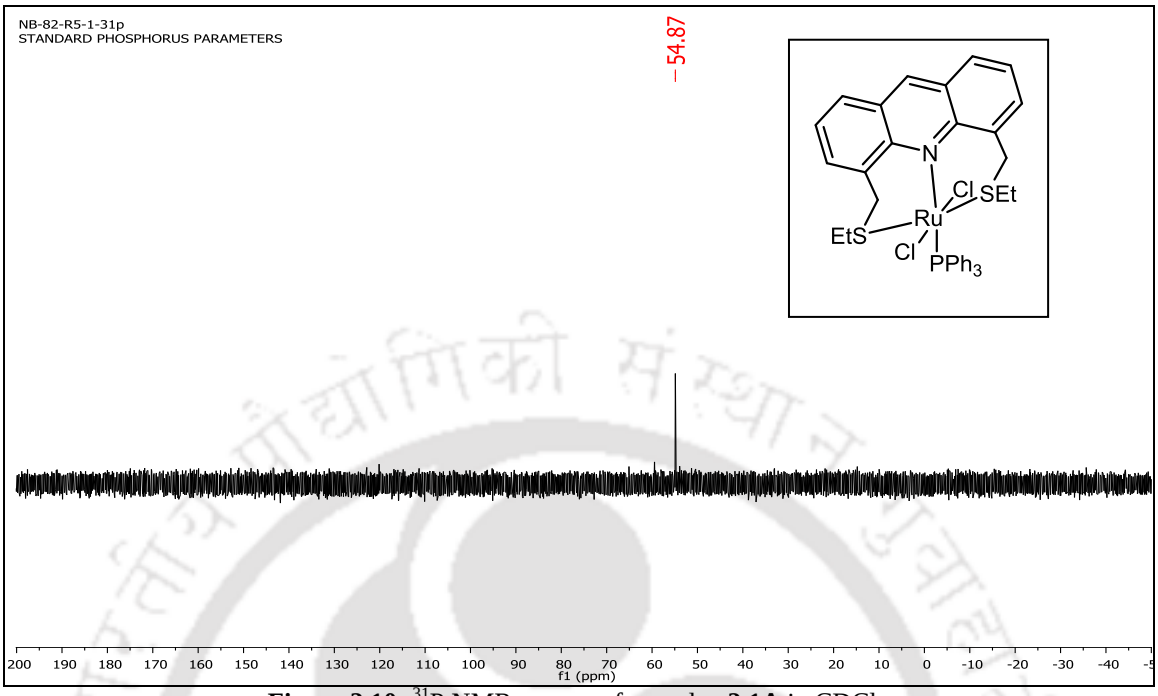

Figure 2.10: ^{31}P NMR spectra of complex **2.1A** in $CDCl_3$

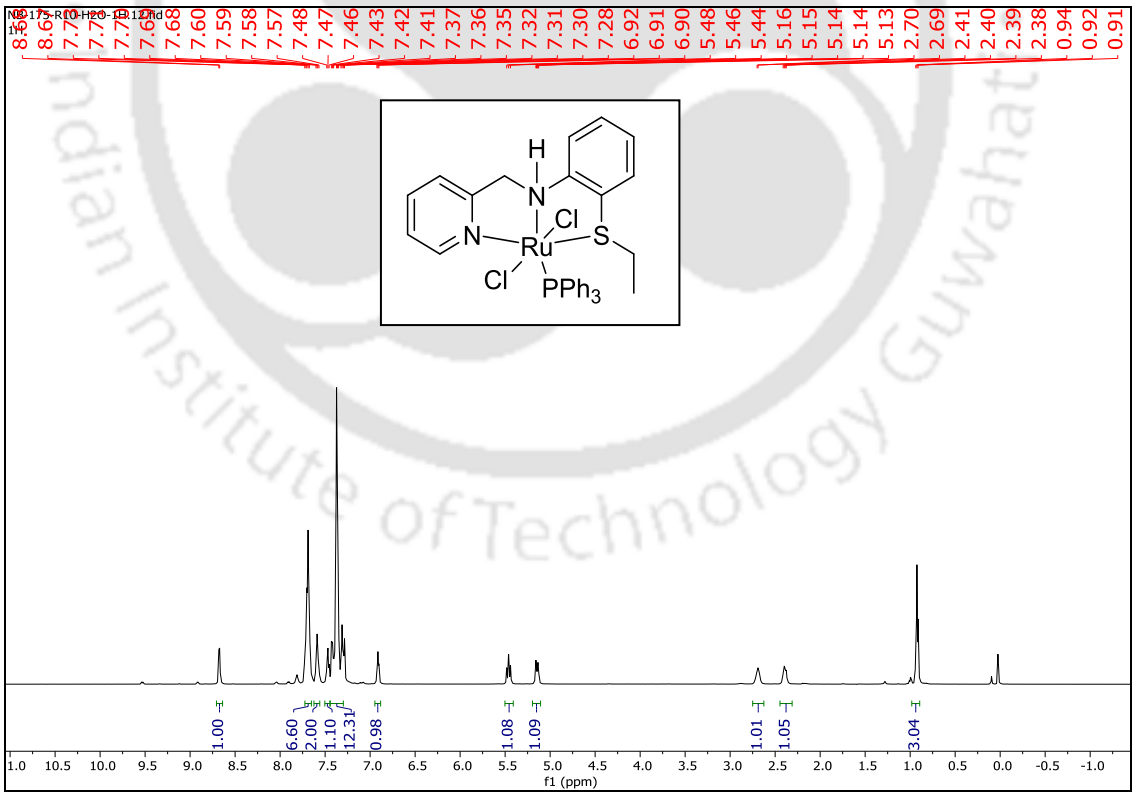

Figure 2.11: ^{1}H NMR spectra of complex **2.2A** in $CDCl_3$

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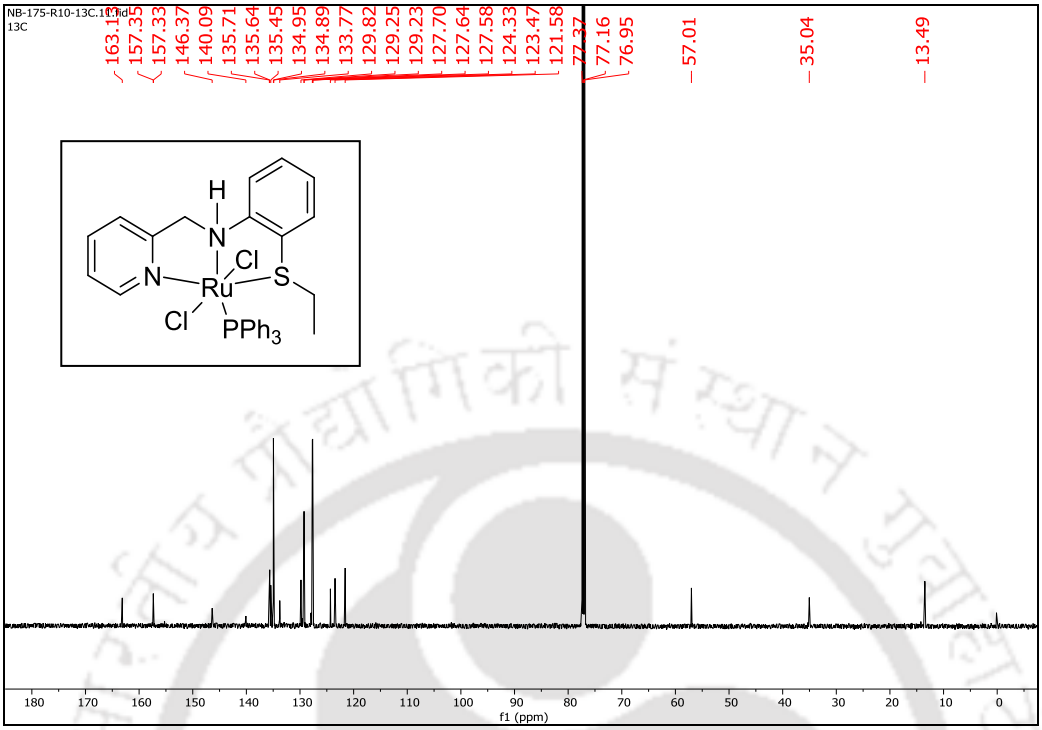

Figure 2.12: ^{13}C NMR spectra of complex **2.2A** in $CDCl_3$

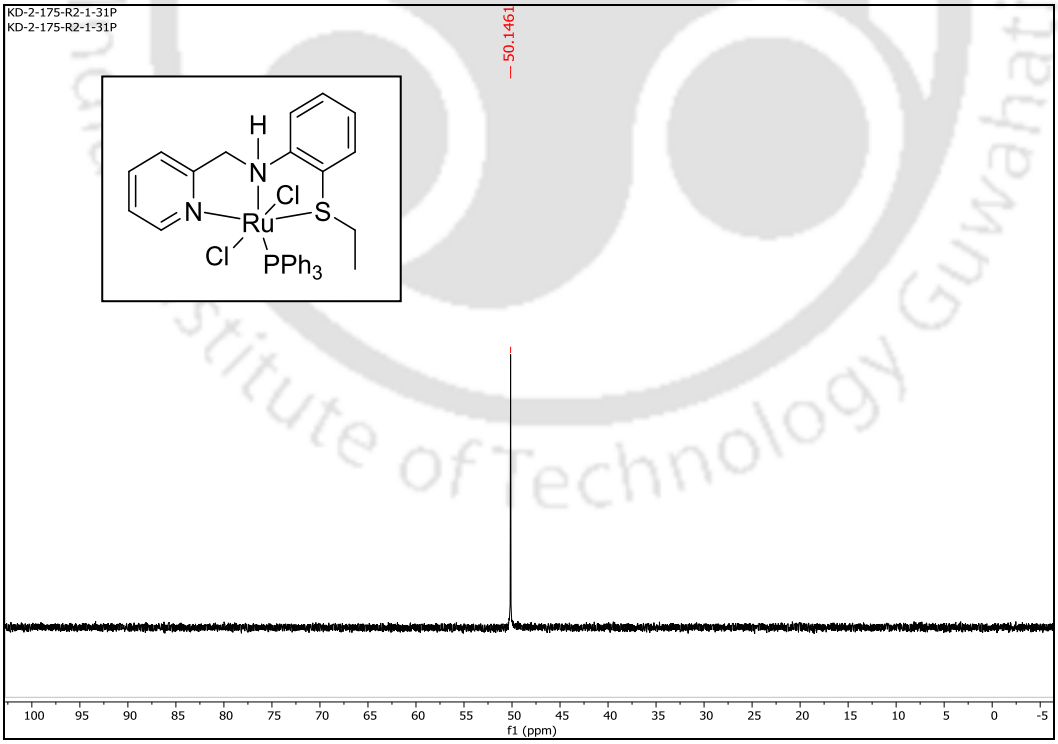

Figure 2.13: ^{31}P NMR spectra of complex **2.2A** in $CDCl_3$

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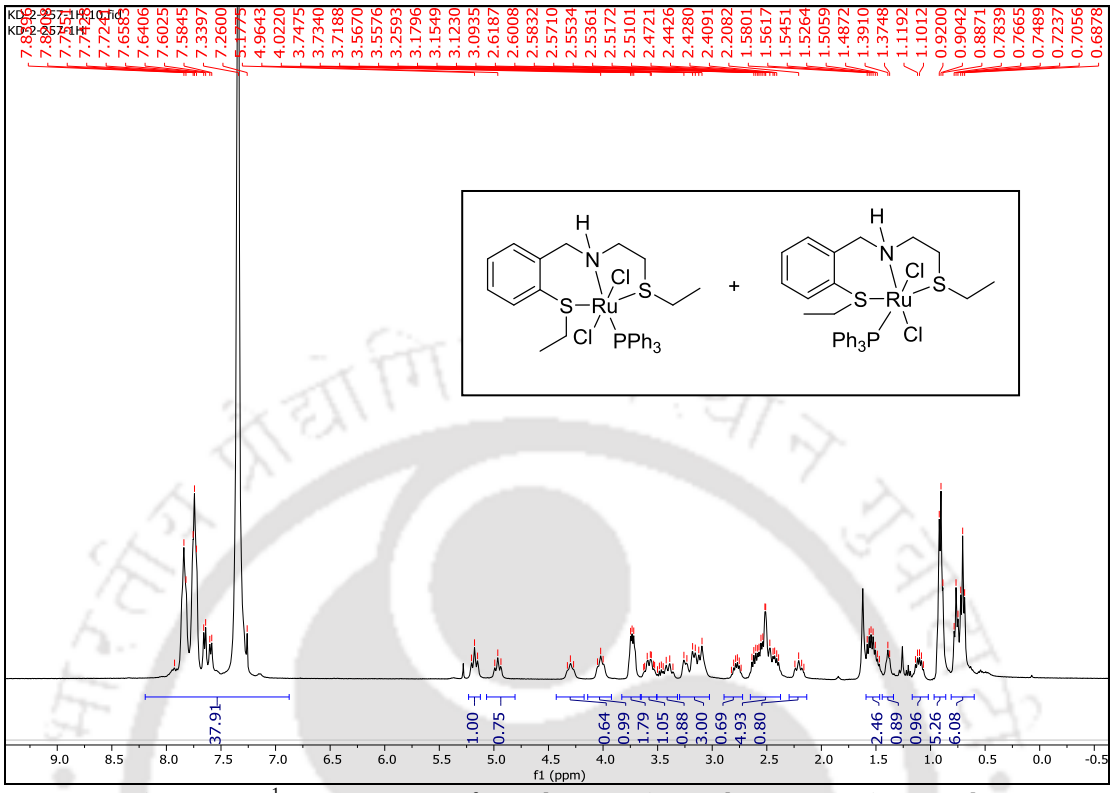

Figure 2.14: ^{1}H NMR spectra of complex **2.3A** (*Cis* and *trans* isomer) in $CDCl_3$

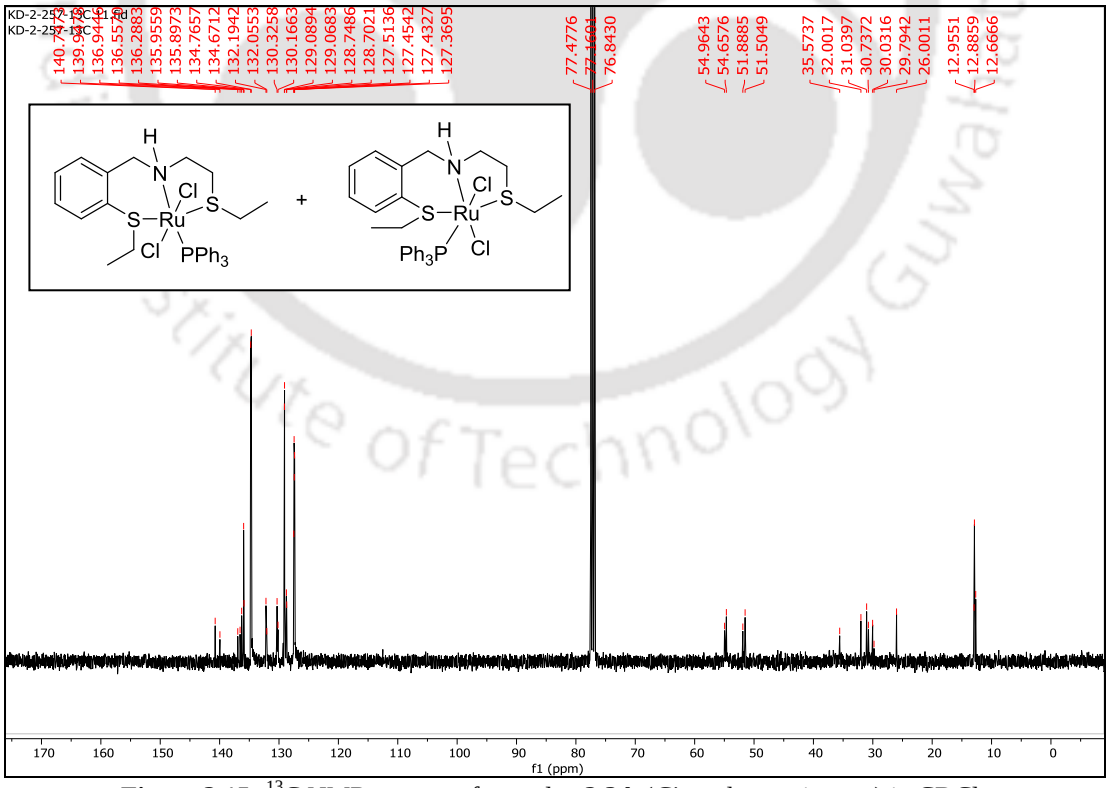

Figure 2.15: ^{13}C NMR spectra of complex **2.3A** (*Cis* and *trans* isomer) in $CDCl_3$

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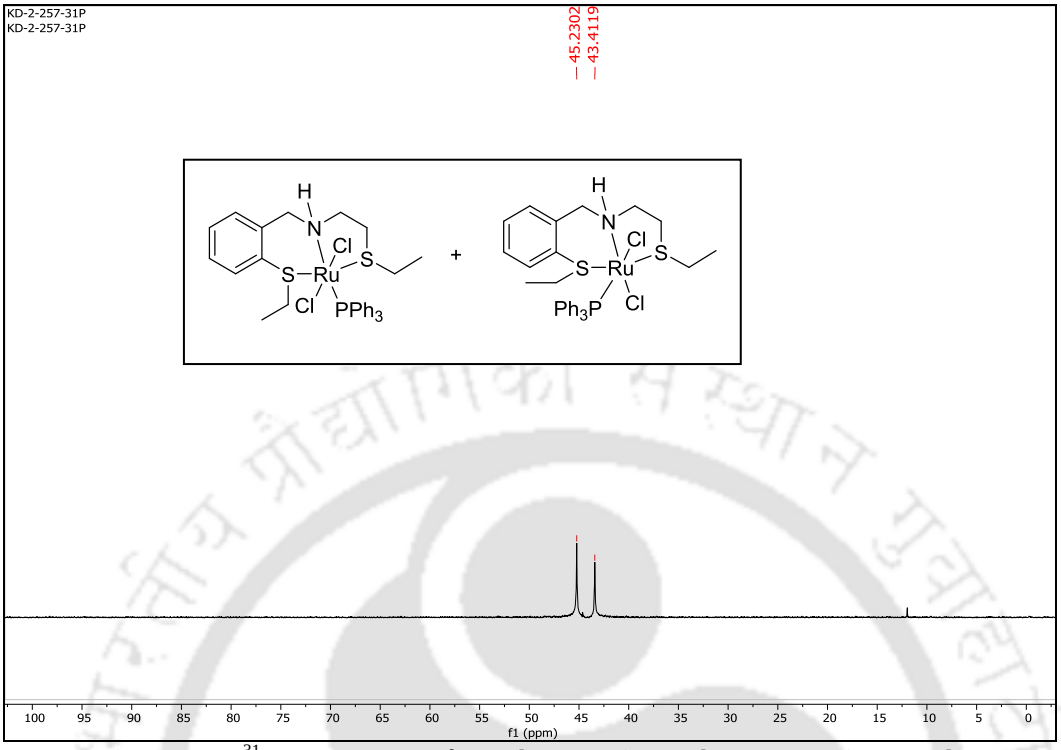

Figure 2.16: ^{31}P NMR spectra of complex **2.3A** (*Cis* and *trans* isomer) in $CDCl_3$

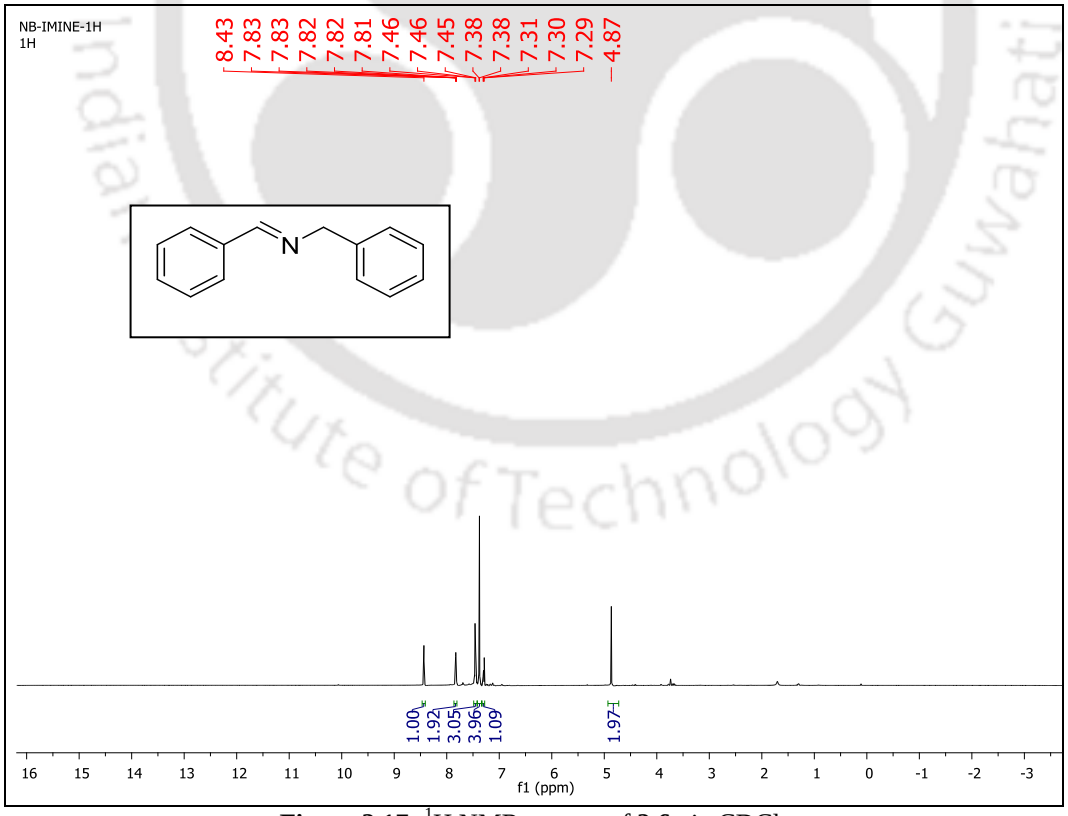

Figure 2.17: ^{1}H NMR spectra of **2.6a** in $CDCl_3$

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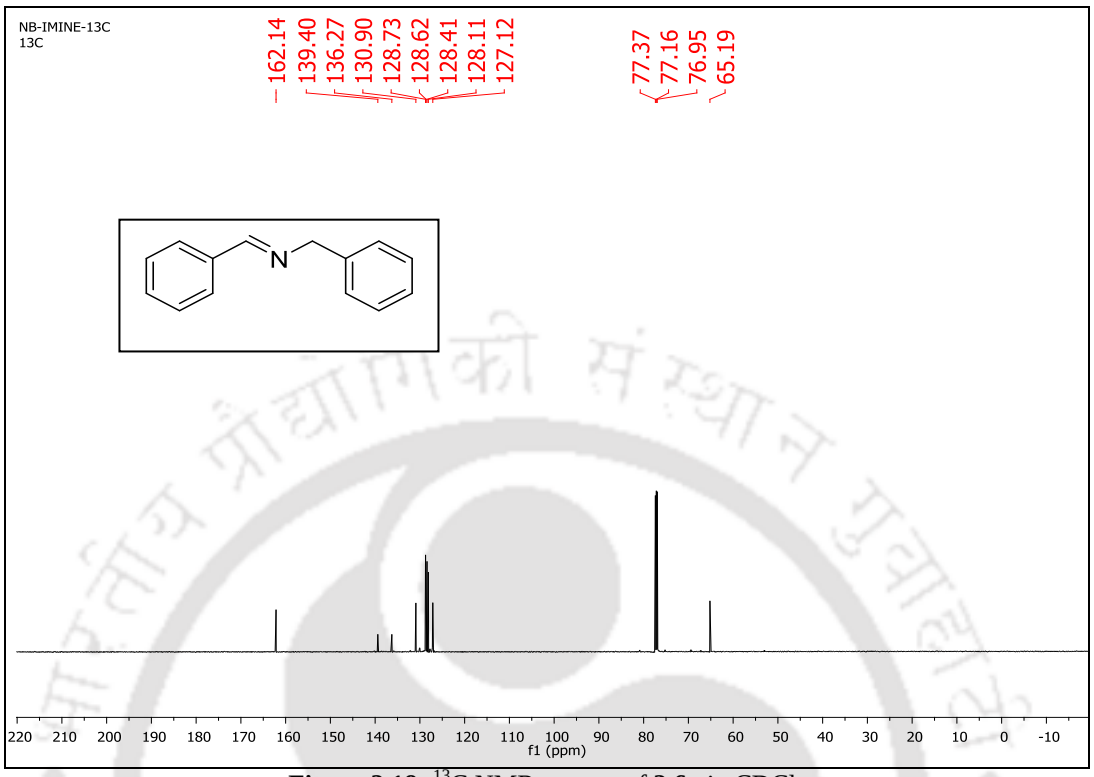

Figure 2.18: ^{13}C NMR spectra of **2.6a** in $CDCl_3$

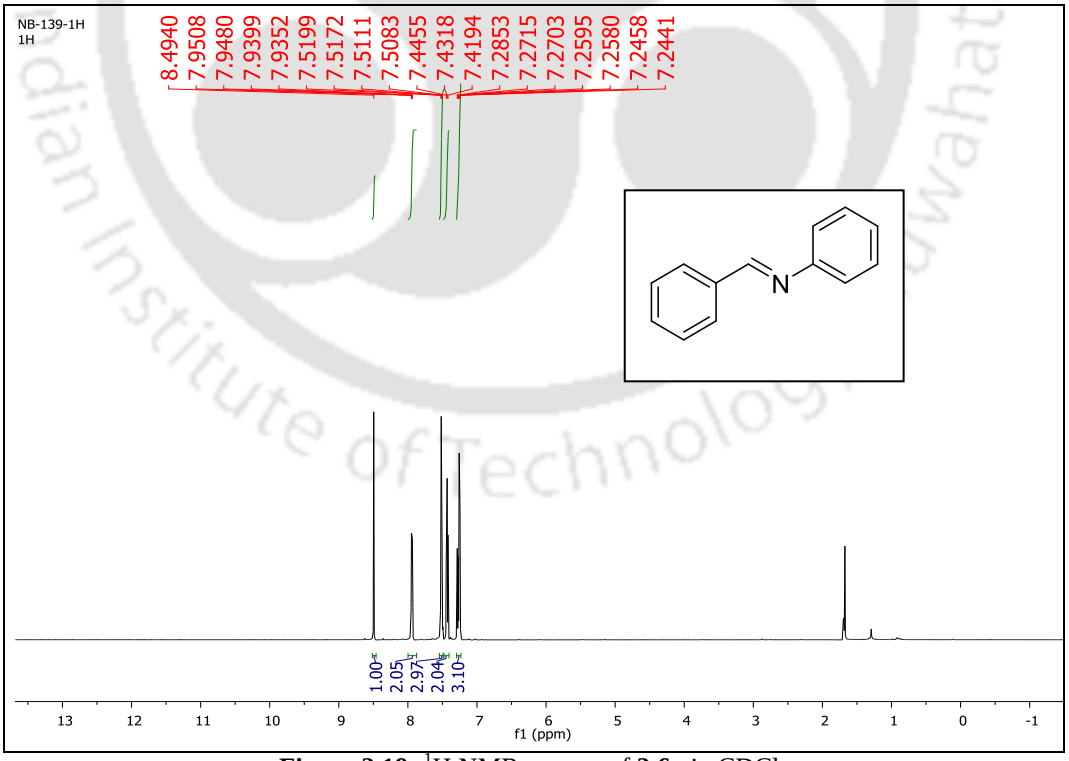

Figure 2.19: ^{1}H NMR spectra of **2.6a** in $CDCl_3$

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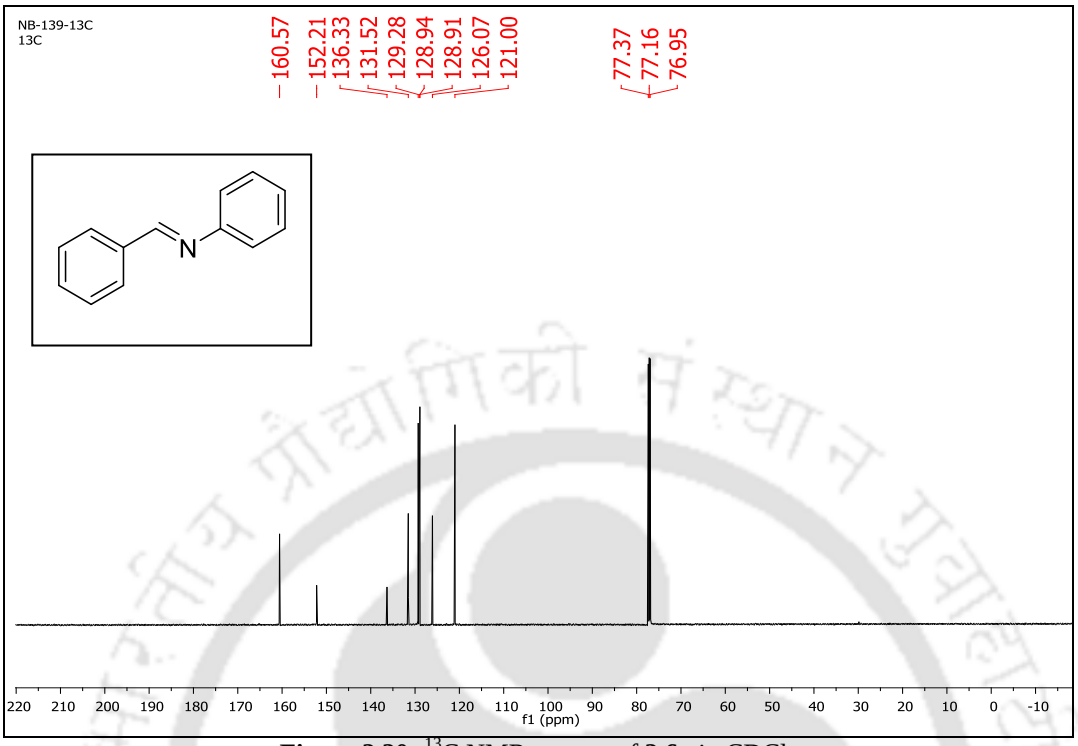

Figure 2.20: ^{13}C NMR spectra of **2.6a** in $CDCl_3$

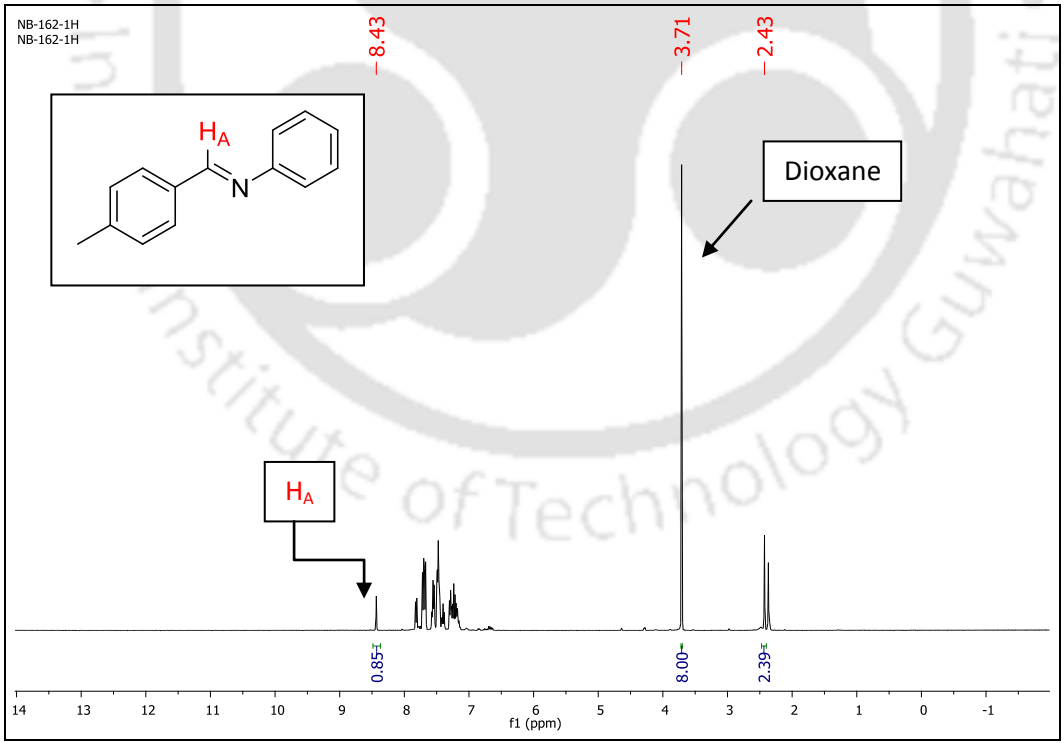

Figure 2.21: Reaction mixture of 4-methylbenzyl alcohol and phenyl azide using dioxane as internal standard in $CDCl_3$

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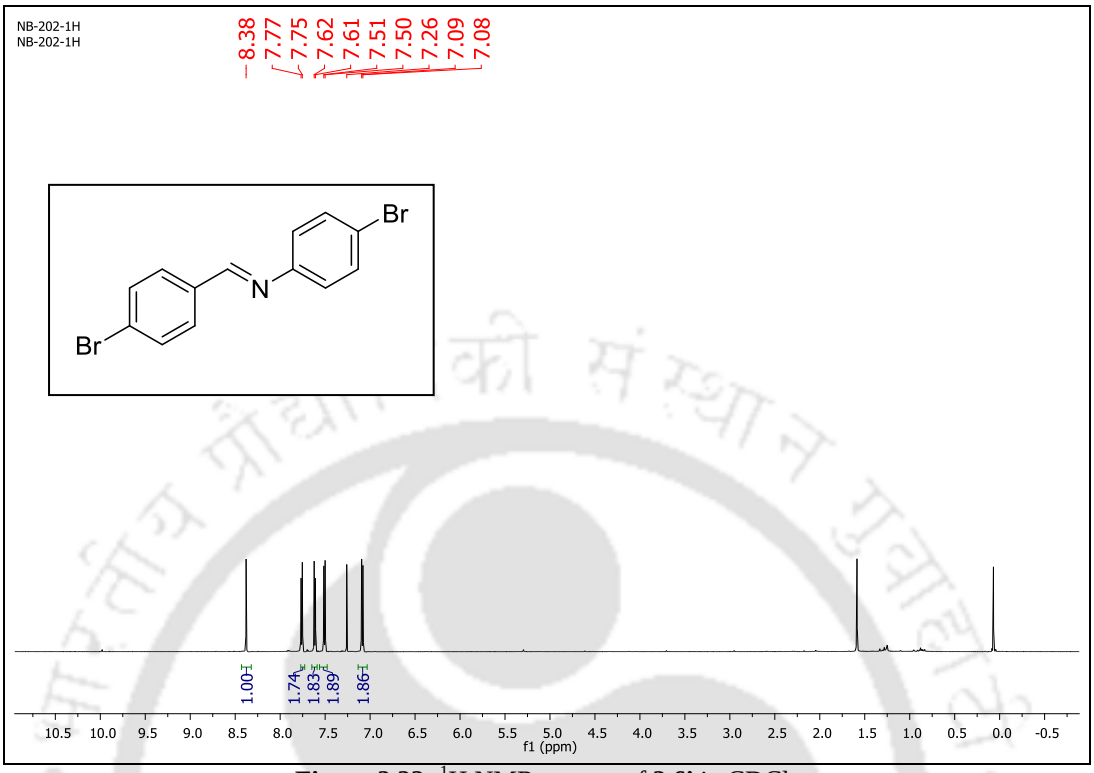

Figure 2.22: ^{1}H NMR spectra of **2.6i** in $CDCl_3$

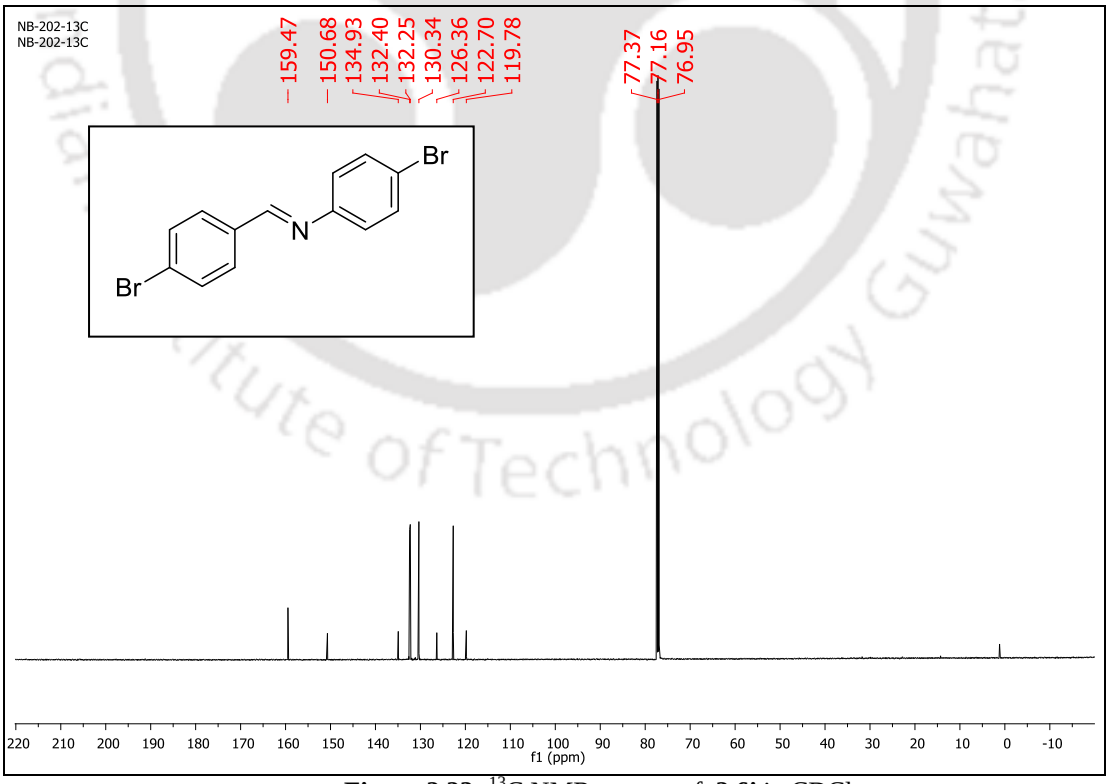

Figure 2.23: ^{13}C NMR spectra of **2.6i** in $CDCl_3$

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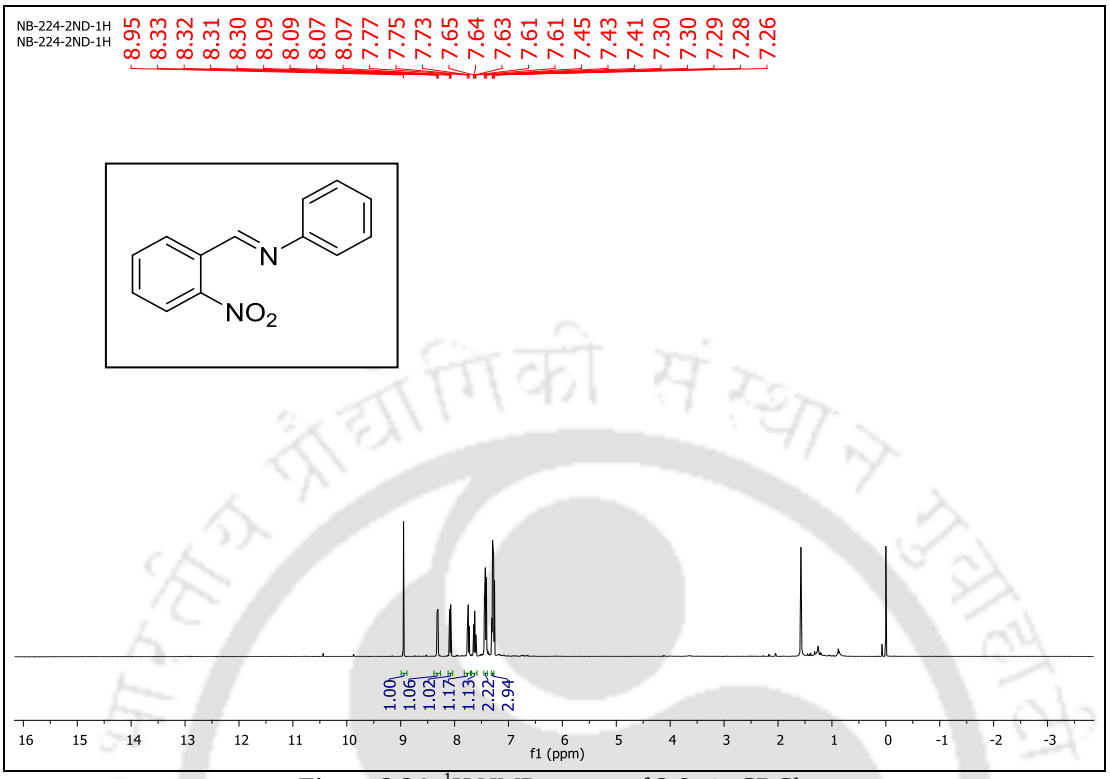

Figure 2.24: ^{1}H NMR spectra of **2.6q** in $CDCl_3$

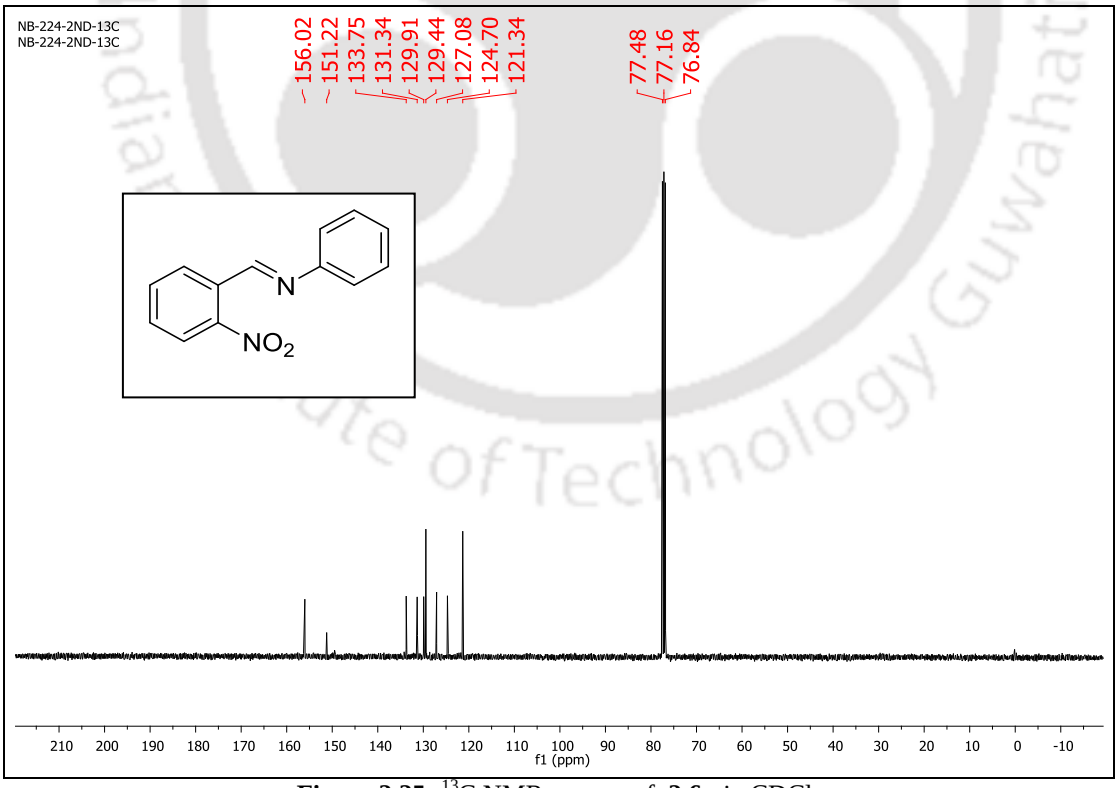

Figure 2.25: ^{13}C NMR spectra of **2.6q** in $CDCl_3$

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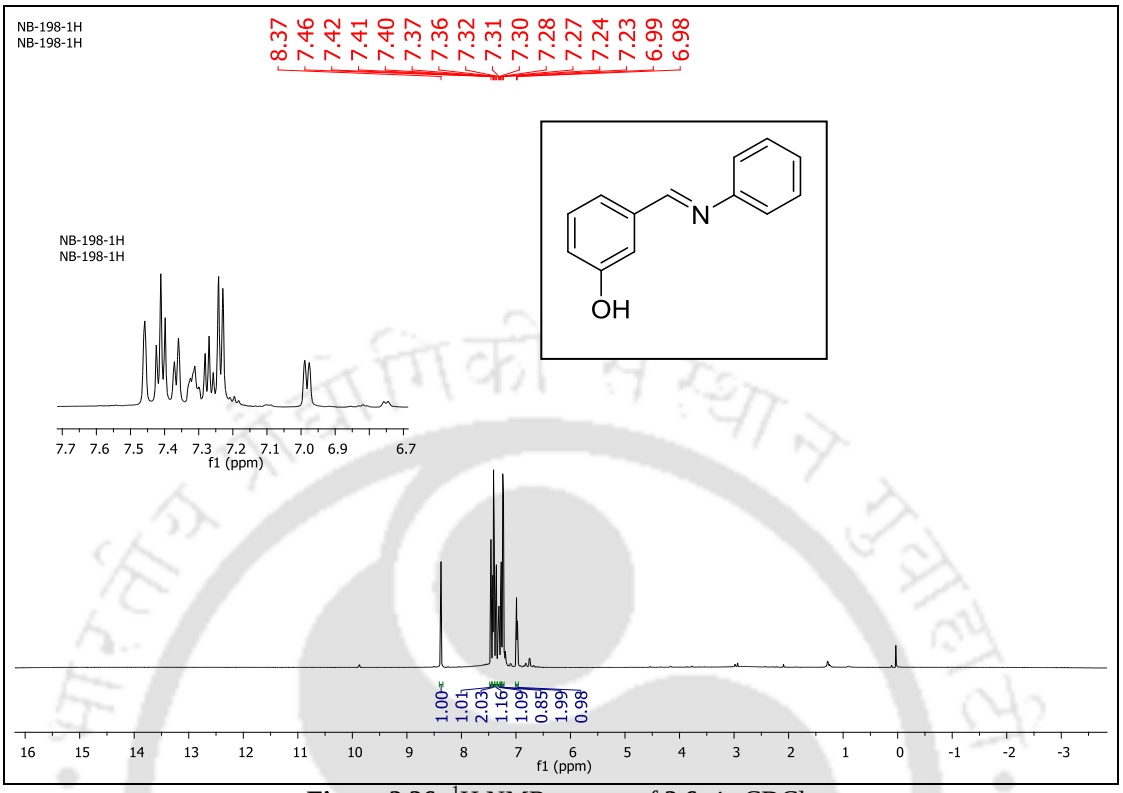

Figure 2.26: ^{1}H NMR spectra of **2.6r** in $CDCl_3$

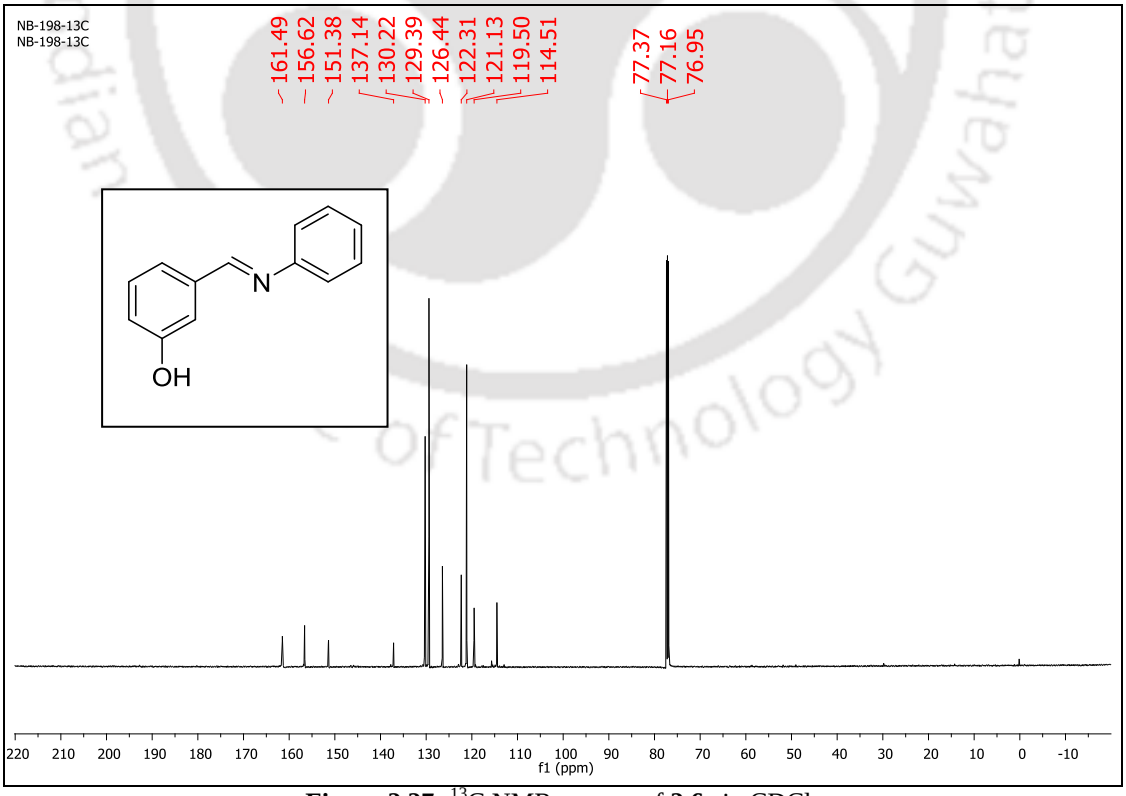

Figure 2.27: ^{13}C NMR spectra of **2.6r** in $CDCl_3$

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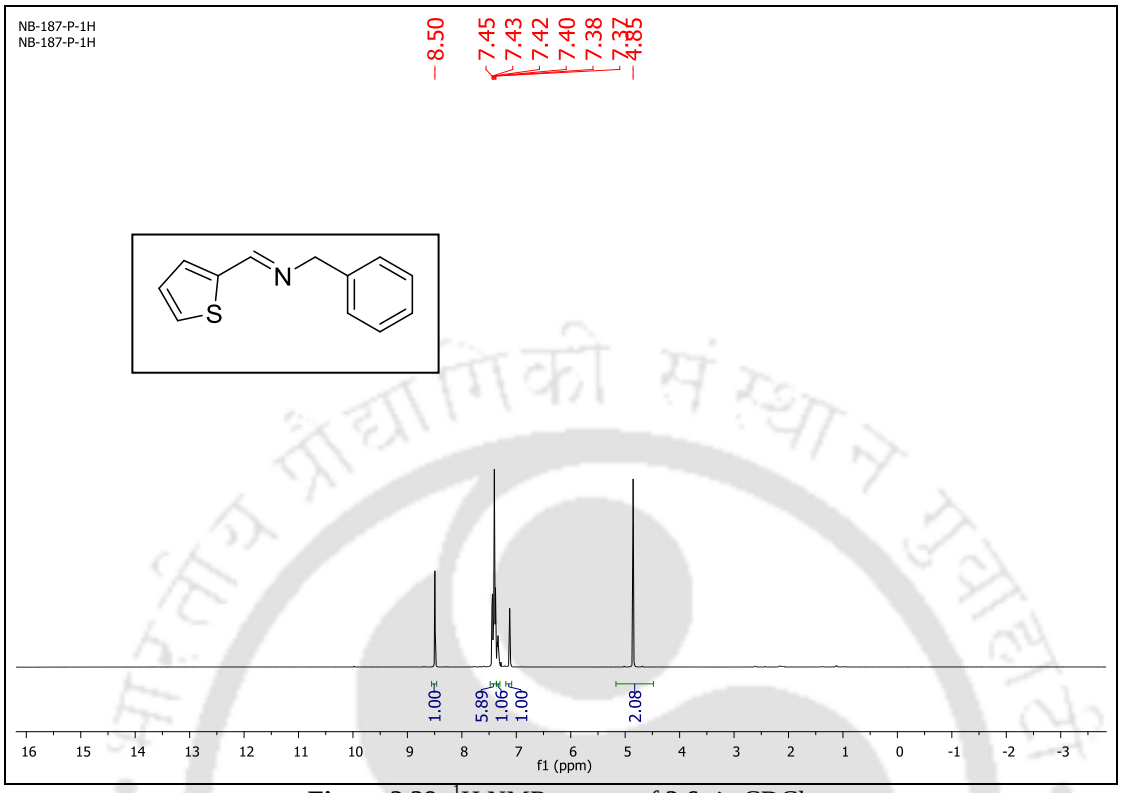

Figure 2.28: ^{1}H NMR spectra of **2.6s** in $CDCl_3$

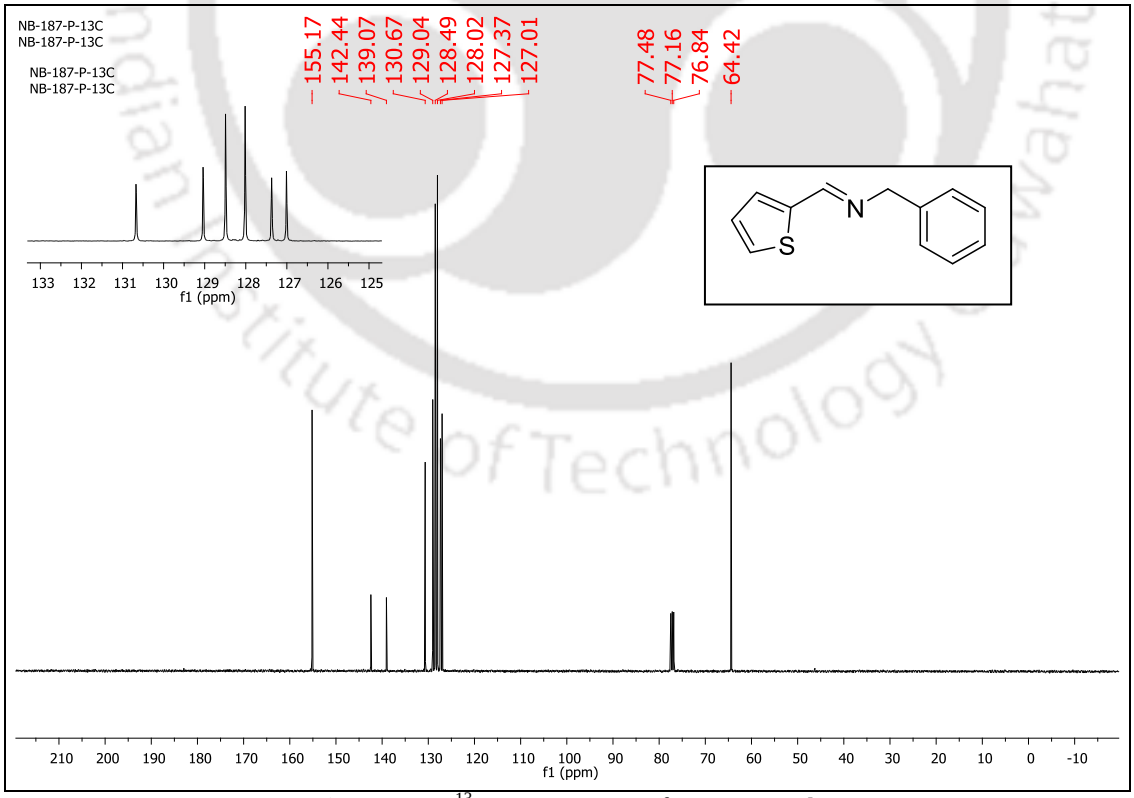

Figure 2.29: ^{13}C NMR spectra of **2.6s** in $CDCl_3$

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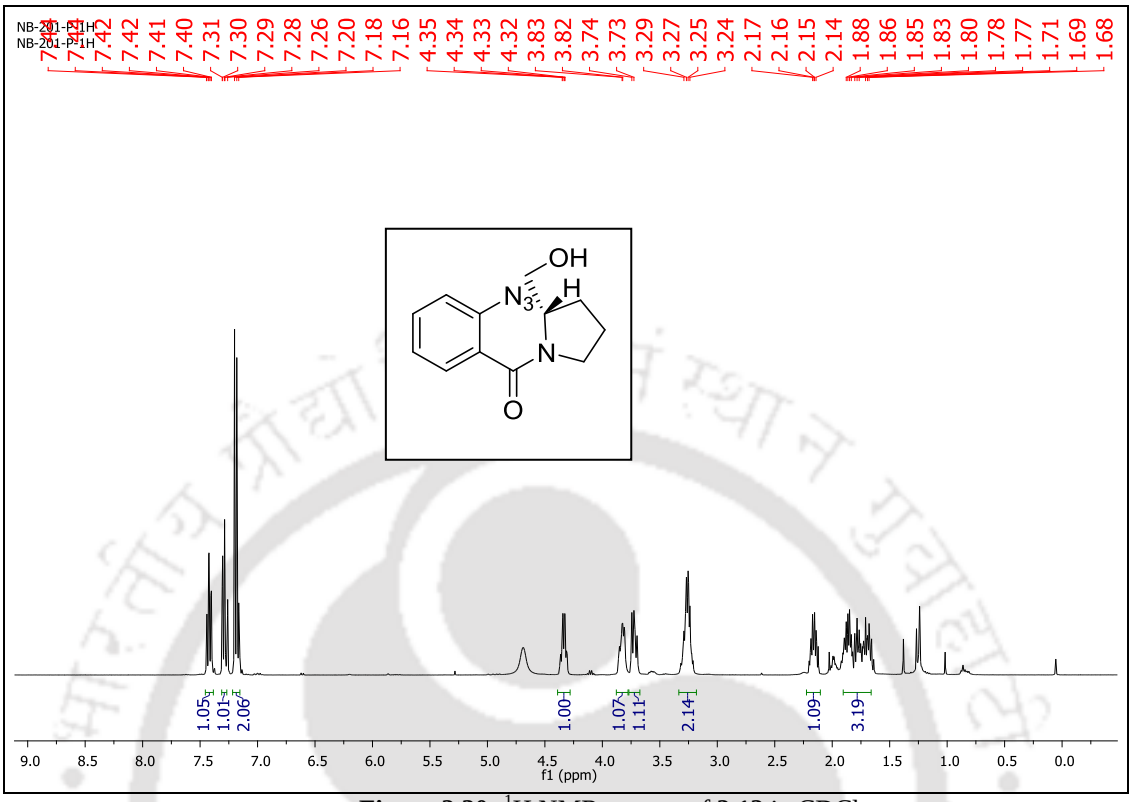

Figure 2.30: ^{1}H NMR spectra of **2.12** in $CDCl_3$

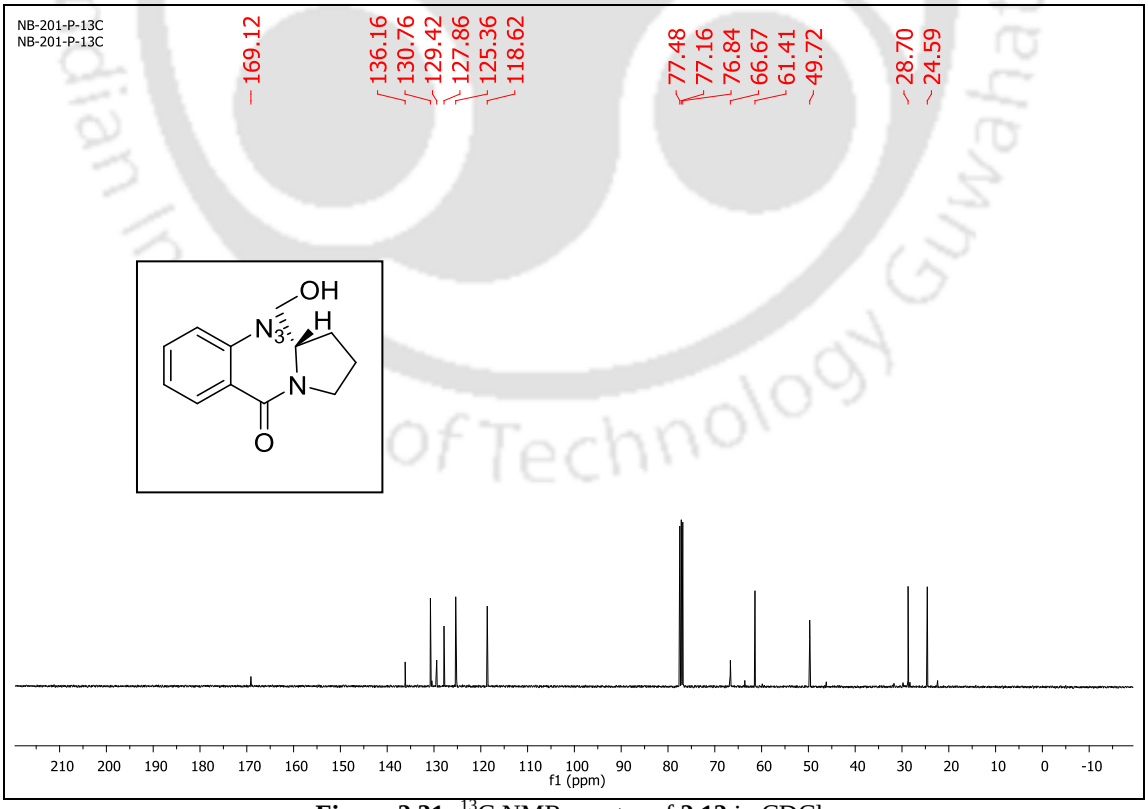

Figure 2.31: ^{13}C NMR spectra of **2.12** in $CDCl_3$

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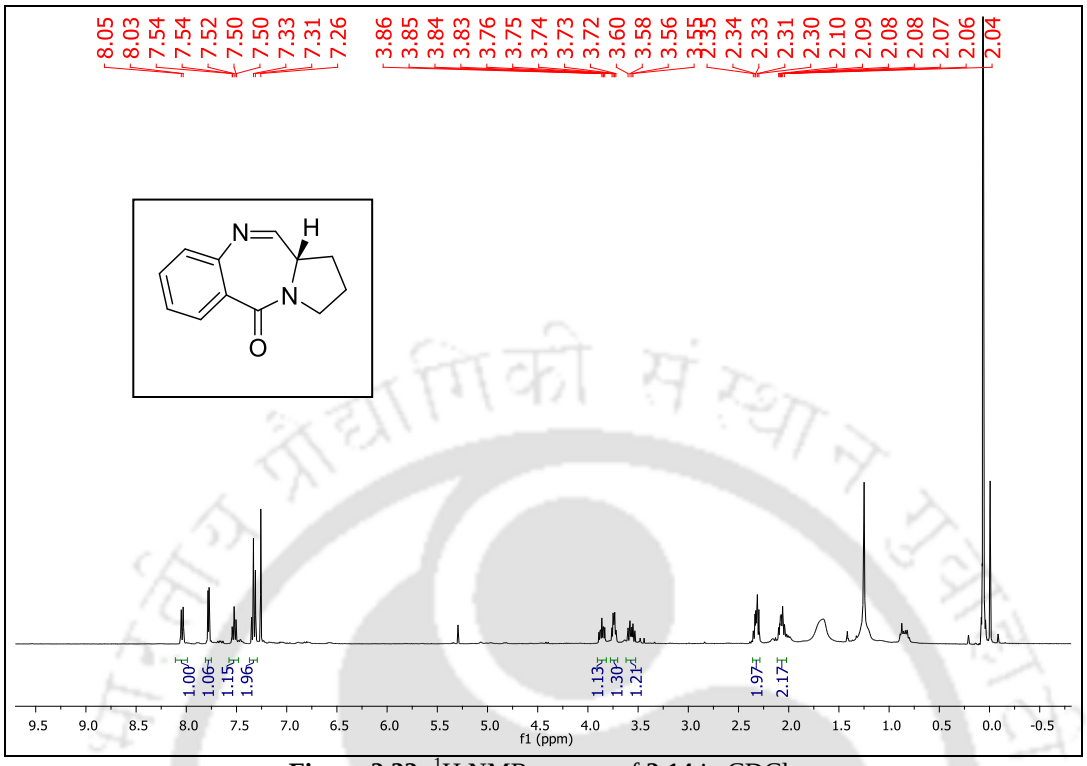

Figure 2.32: ^{1}H NMR spectra of **2.14** in $CDCl_3$

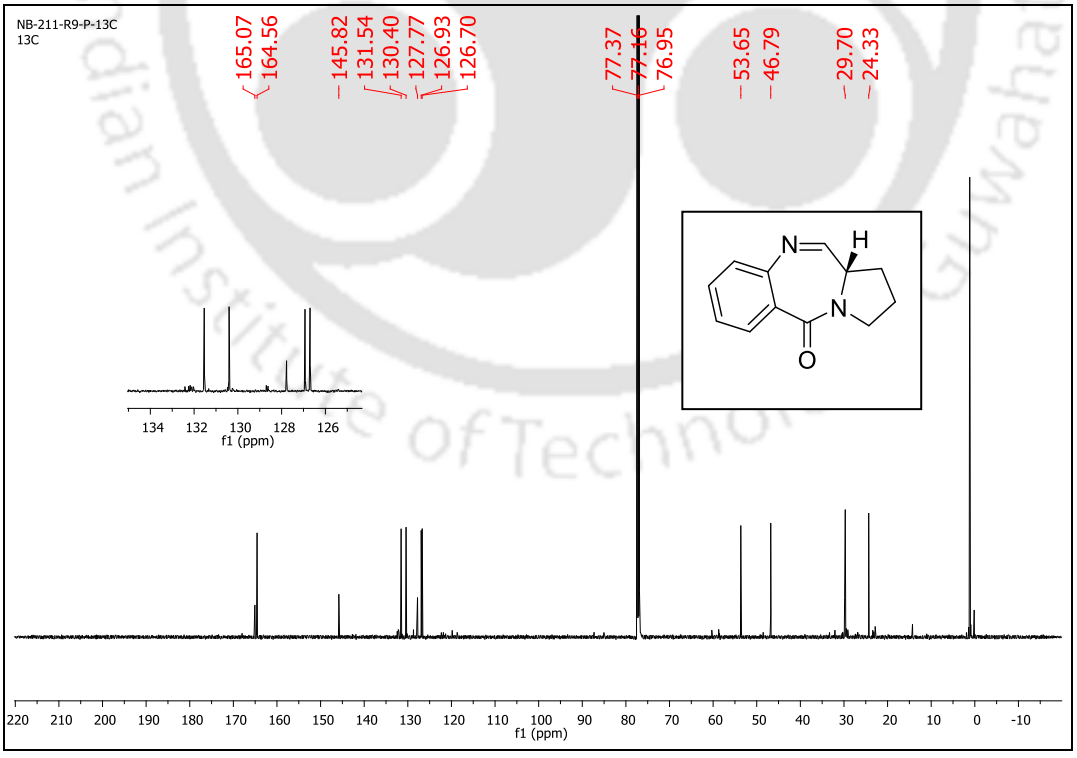

Figure 2.33: ^{13}C NMR spectra of **2.14** in $CDCl_3$

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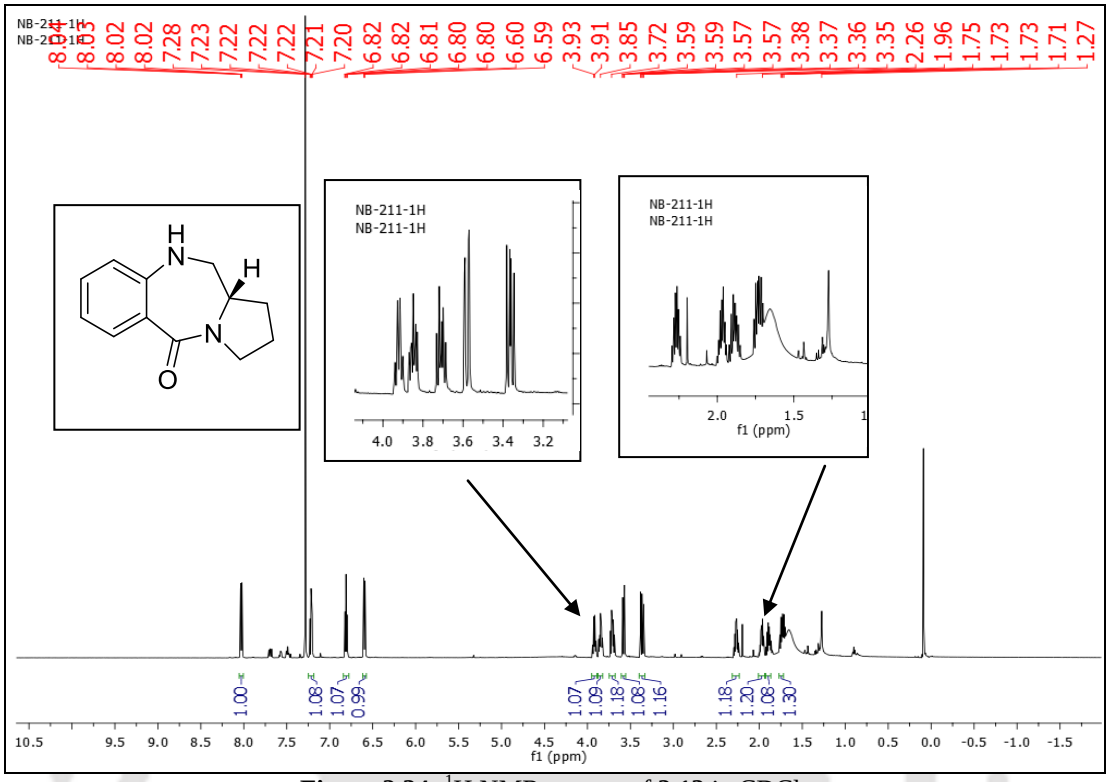

Figure 2.34: ^{1}H NMR spectra of **2.13** in $CDCl_3$

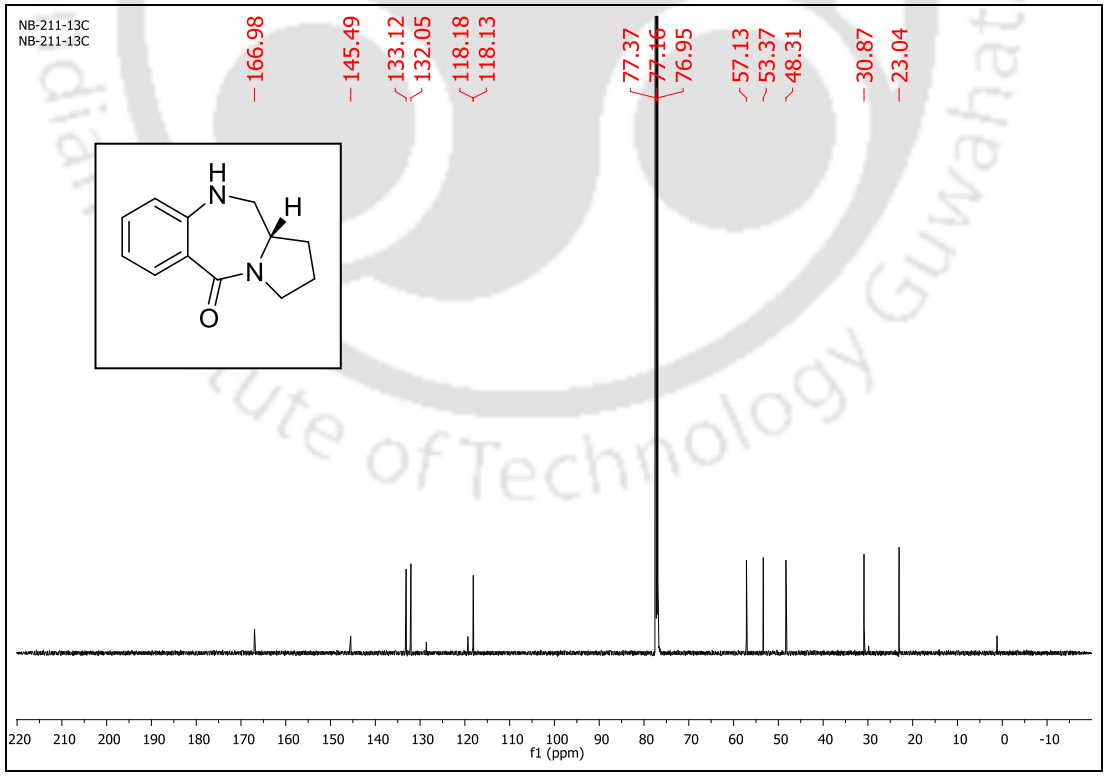

Figure 2.35: ^{13}C NMR spectra of **2.13** in $CDCl_3$

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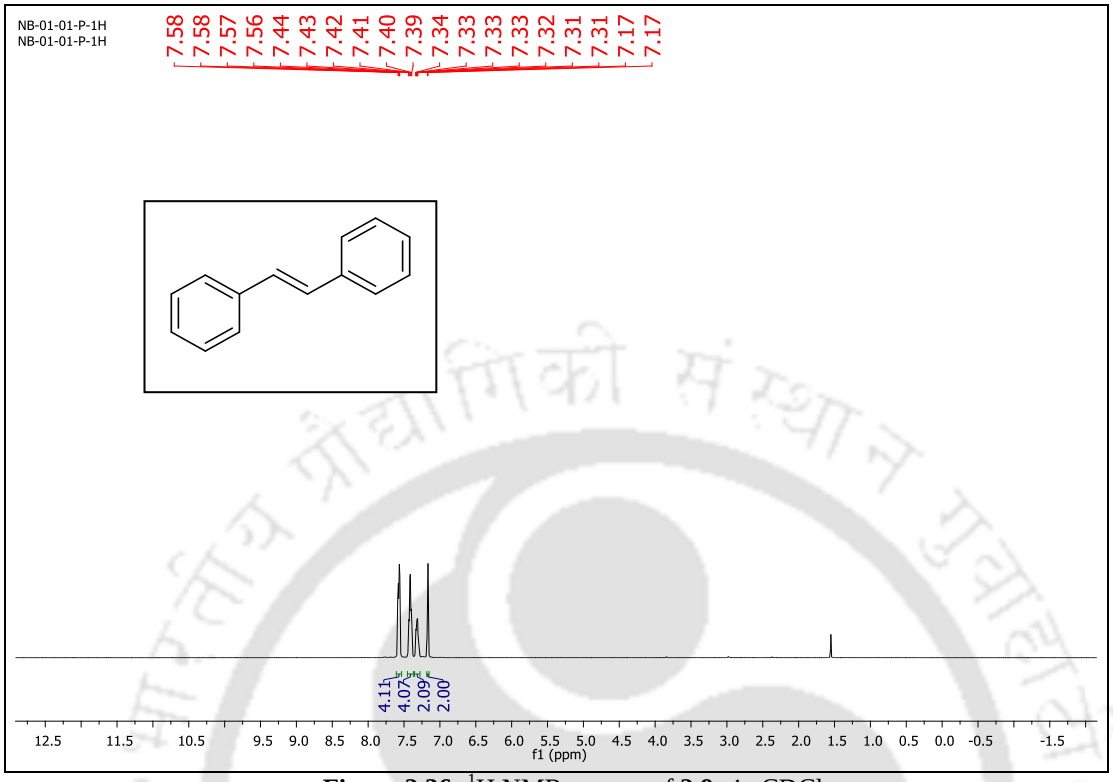

Figure 2.36: ^{1}H NMR spectra of **2.9a** in $CDCl_3$

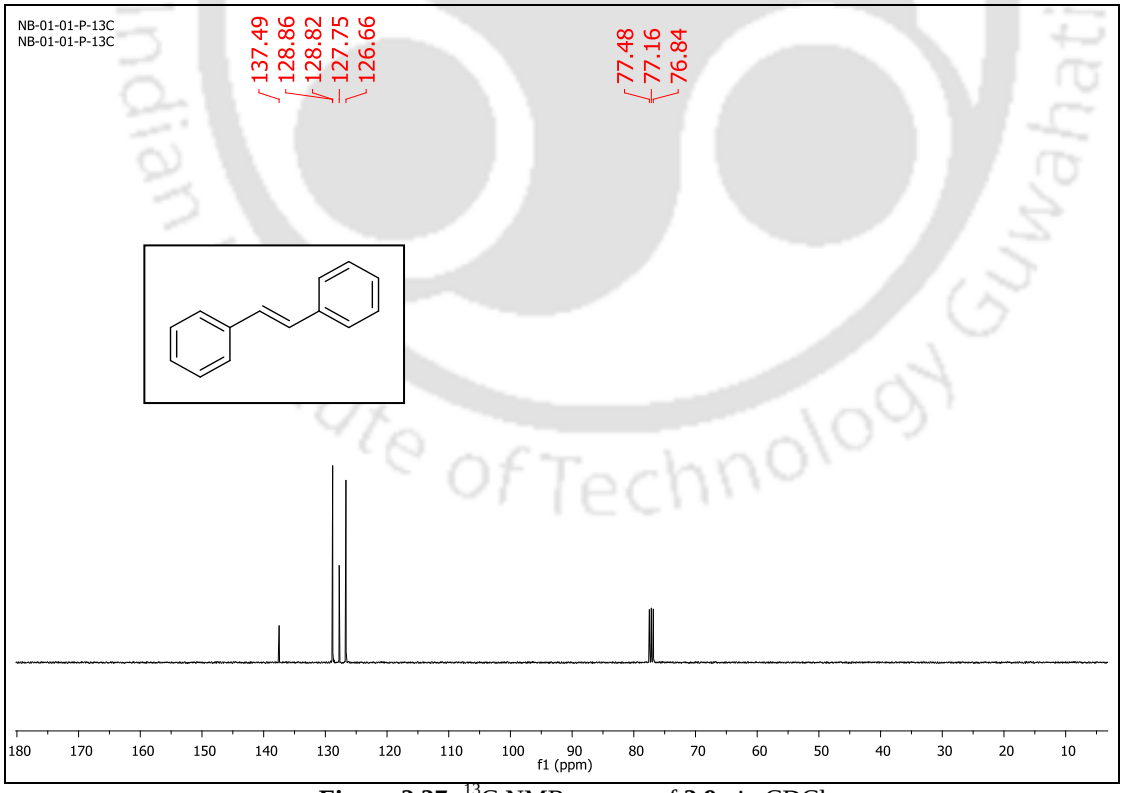

Figure 2.37: ^{13}C NMR spectra of **2.9a** in $CDCl_3$

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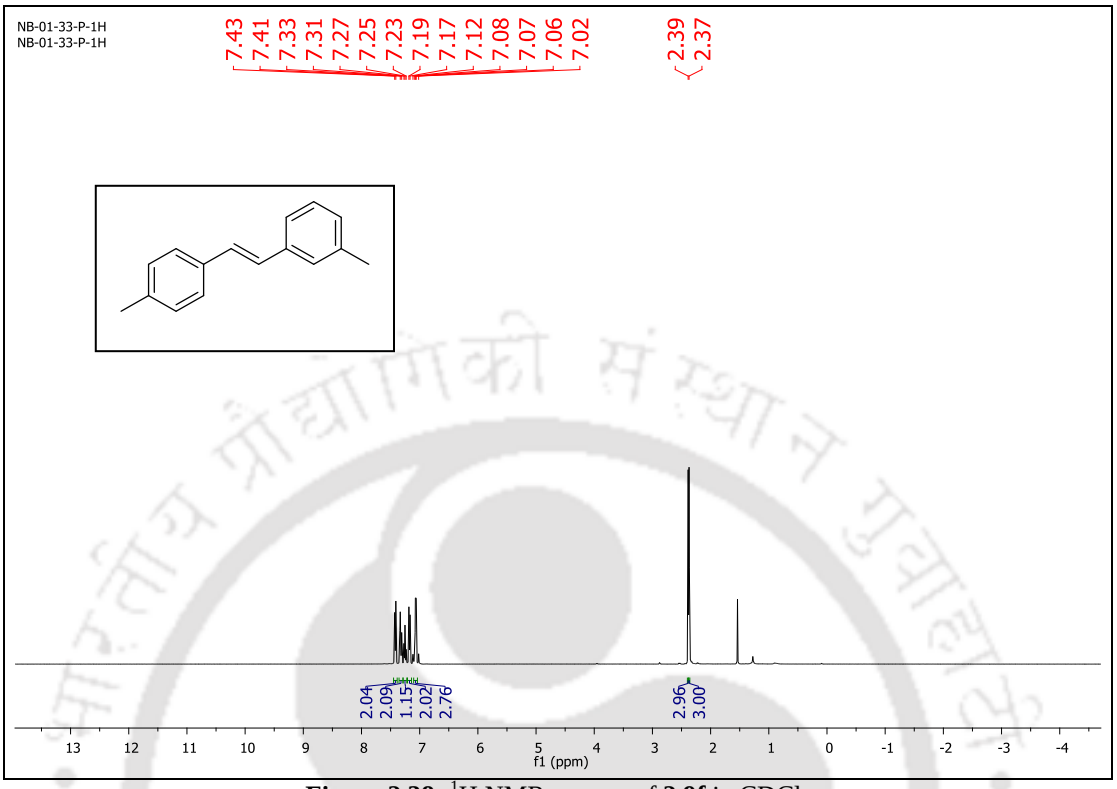

Figure 2.38: ^{1}H NMR spectra of **2.9f** in $CDCl_3$

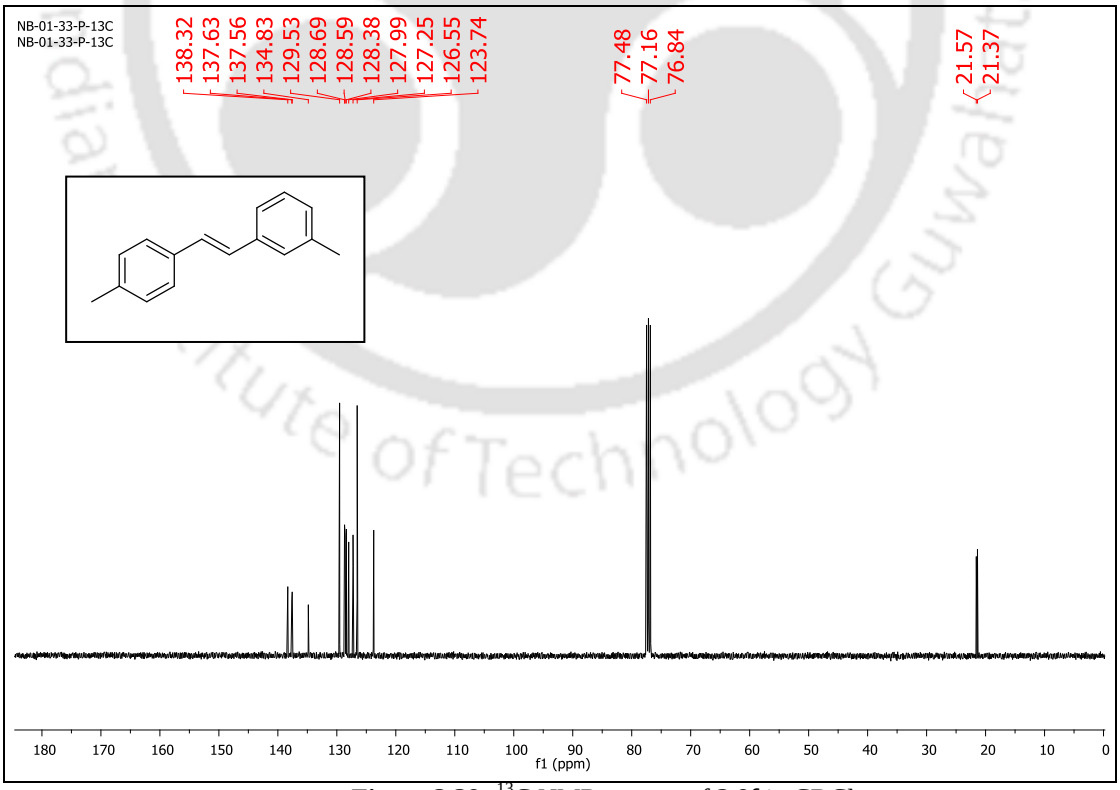

Figure 2.39: ^{13}C NMR spectra of **2.9f** in $CDCl_3$

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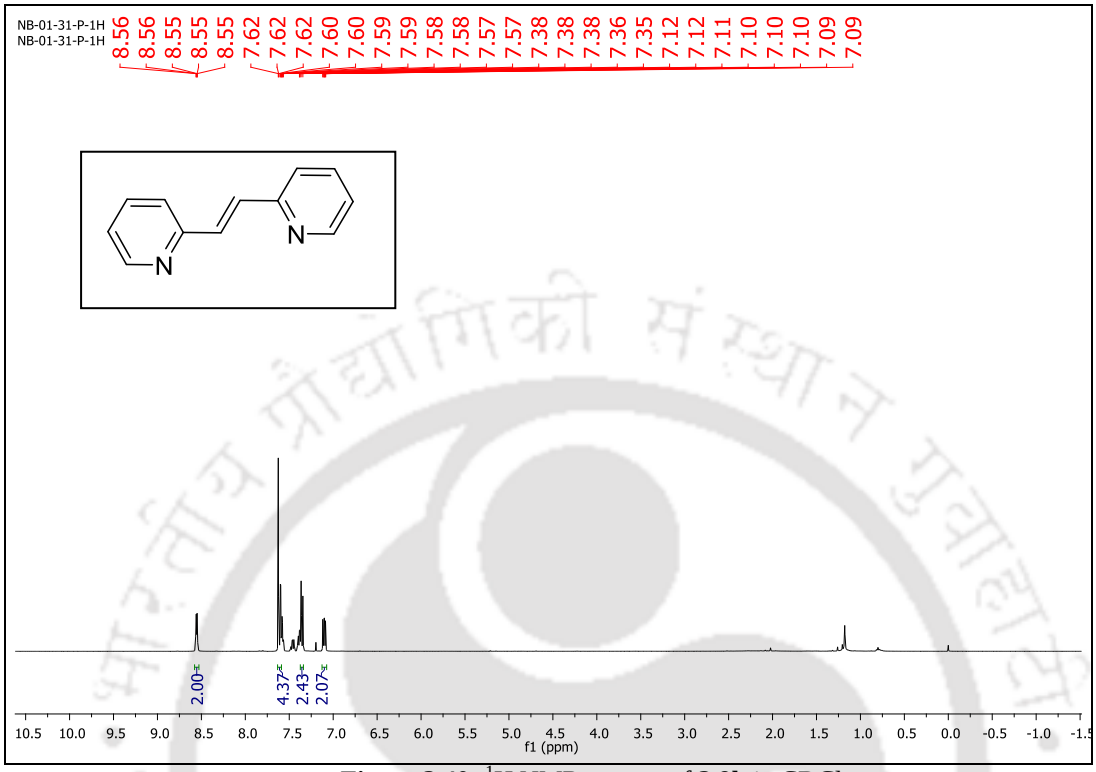

Figure 2.40: ^{1}H NMR spectra of **2.9h** in $CDCl_3$

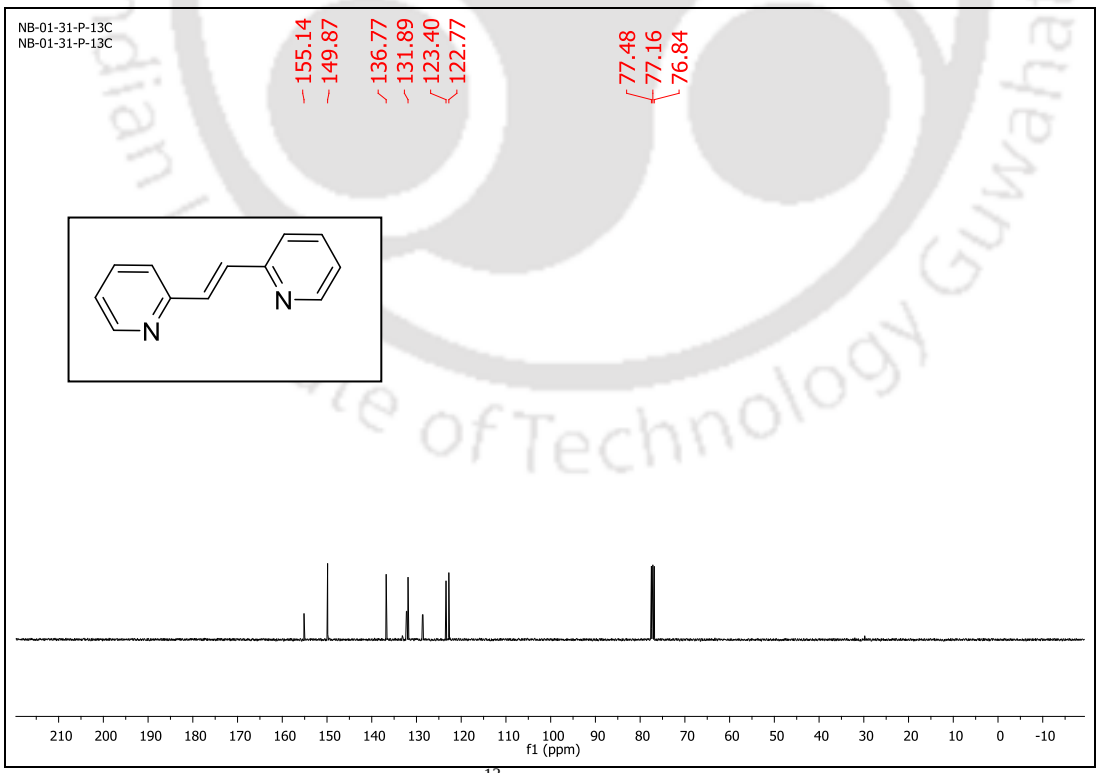

Figure 2.41: ^{13}C NMR spectra of **2.9h** in $CDCl_3$

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Chapter 3

Synthesis of 1,8-dioxo-decahydroacridine derivatives via Ru-Catalysed Acceptorless Dehydrogenative Multicomponent Reaction (ADMCR)

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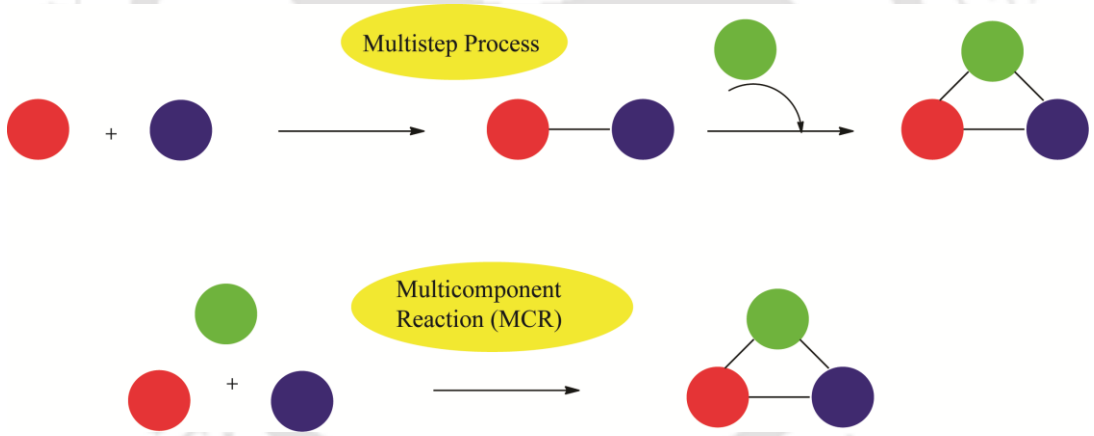
3.1. Introduction:

Multicomponent reactions (MCRs)[1] have received a great deal of interest for the implementation of new processes and new synthetic strategies. One-pot multicomponent coupling reactions (MCRs), where several organic moieties are coupled in one-step for C-C and C-heteroatom (N, S, O) bond formation, is an attractive synthetic strategy for the synthesis of the large important heteroaromatic molecules. Thus, MCRs because of their substantial advantages over the conventional multi-step approaches have received significant attention in organic synthesis (Scheme **3.1**). MCRs are considered to be green in terms of productivity, energy saving, and step-economy.[2] Therefore, the recent years witnessed an exponential growth in the area of multicomponent reaction[3] strategies for the synthesis of heterocycles *via* successive formation of C-C and C-heteroatom bonds.[4]



Scheme 3.1: General strategy of multicomponent reaction (MCR)

The replacement of toxic as well as waste generating reagents with greener and renewable feedstock is another major aspect of green chemistry.[5] In this regards alcohols are considered as greener alternative feedstock as it is obtained from various natural sources especially from biomass.[6] Hence the last decades witnessed an extensive utilization of alcohols in organic synthesis *via* "acceptorless dehydrogenation (AD)"[7] or "borrowing hydrogen (BH)" catalysis.[8] Thus, the synthesis of useful heteroaromatic

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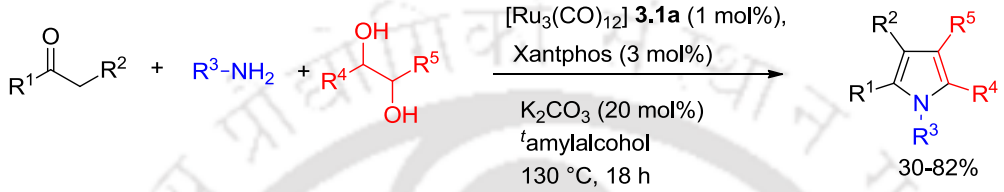
compounds *via* acceptorless dehydrogenative multicomponent reactions (ADMCRs)[4b,9] is considered as a highly environmentally benign, atom economical and cost-effective approach. In this context, *Beller and coworkers* demonstrated a unique ADMCR approach to synthesize pyrroles *via* one-pot three-component (ketones, amines and 1,2-diols) coupling.[9a-b]



Scheme 3.2: Synthesize pyrroles *via* one-pot three-component

Kempe[9c,9d] and *Kirchner*[9e] independently demonstrated the synthesis of pyrimidines *via* ADMCR strategy. In 2015, *Kempe*[9c] has shown a novel iridium-catalyzed (**1.3i**) multicomponent pyrimidine synthesis by the combination of 1° alcohol, 2° alcohol and amidine. In the course of this sustainable three component coupling reaction, 2 equiv of hydrogen and water were liberated. They also illustrated a consecutive 4-component coupling for pyrimidine synthesis. In the approach first the "secondary carbon atom" is formed by selective *β*-alkylation of the methyl group of 1-substituted ethanol derivative. After that addition of third alcohol and the amidine building block gives rise to a fully substituted pyrimidine derivative (Scheme **3.3**). In 2016, *Kirchner*[9e] applied manganese complex **1.3k** to catalyze three-component pyrimidine synthesis. In 2017, *Kempe*[9d] utilized manganese catalyst **1.3e** to illustrate three and four component pyrimidine synthesis.

The group of *Milstein*[9f] illustrated the synthesis of *N*-substituted pyrroles *via* one pot synthesis of NH-pyrroles followed by *N*-alkylation (Scheme **3.4**). First, alcohol and ammonia get reacted to form benzyl amine derivative. After that, benzyl amine reacted with in situ formed 1,4-diketone *via* dehydrogenation of 1,4-diol to afford the *N*-alkylated pyrrole product. If, the ammonia directly react with the in situ formed 1,4-diketone, then it will give NH-pyrrole derivative which is the small side product of this reaction. Therefore, two competitive reactions can take place in this approach and it was

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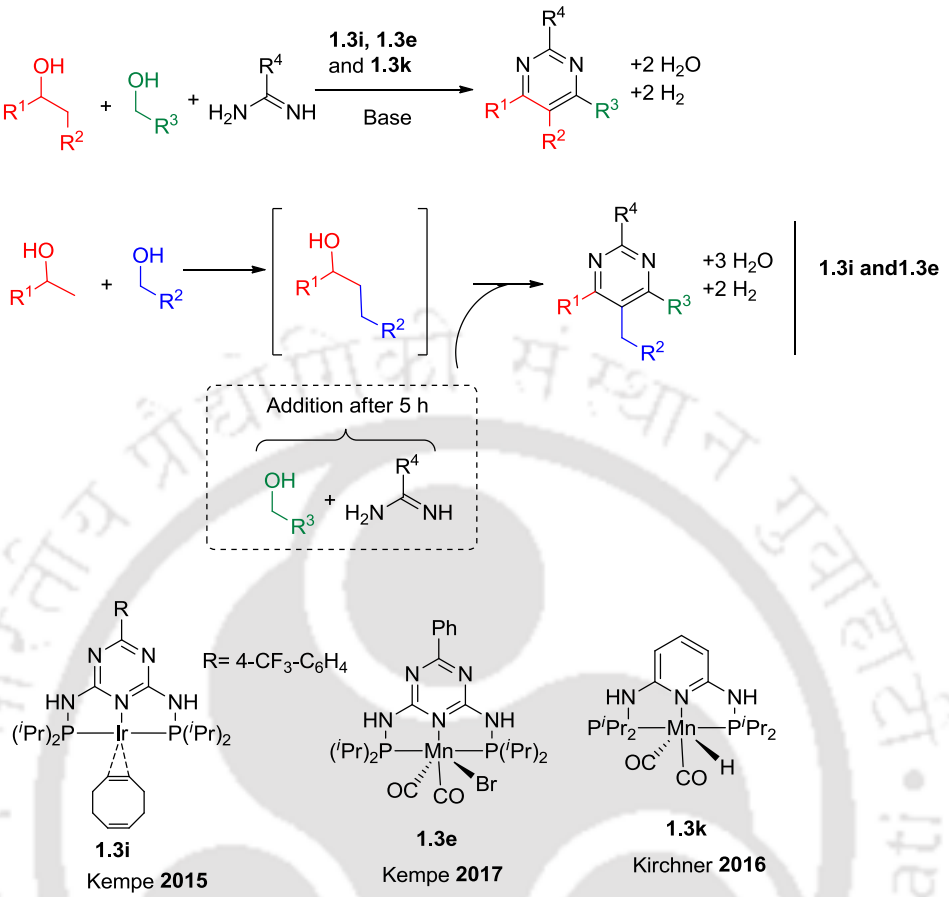
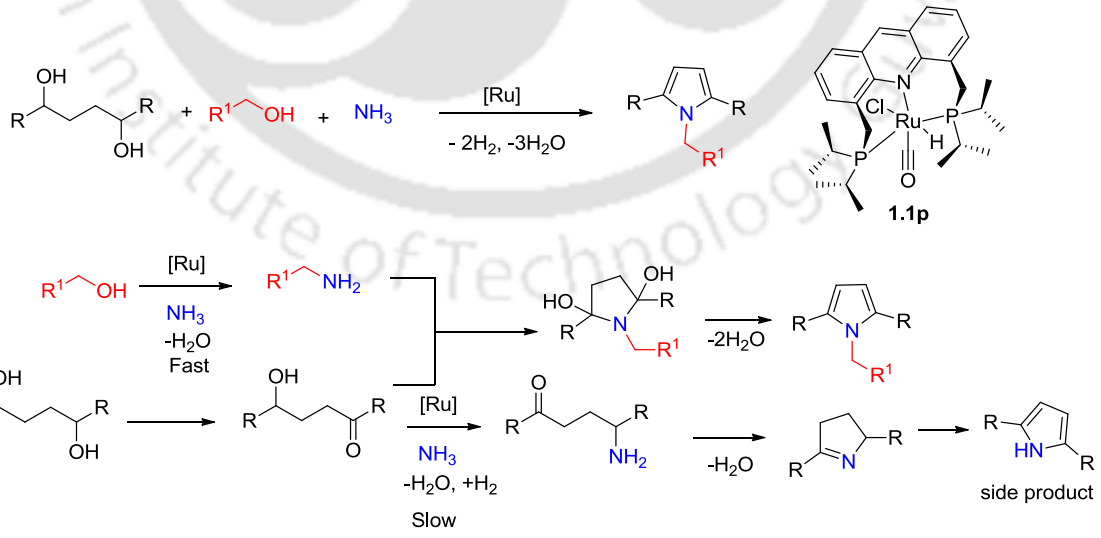


Scheme 3.3: Synthesis of pyrimidines *via* ADMCR strategy using Ir and Mn complex



Scheme 3.4: Synthesis of *N*-alkylated pyrrole *via* ADMCR

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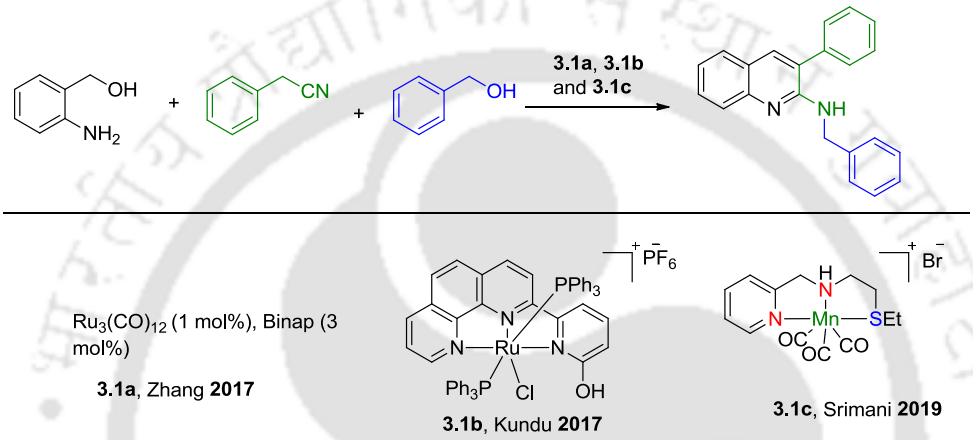
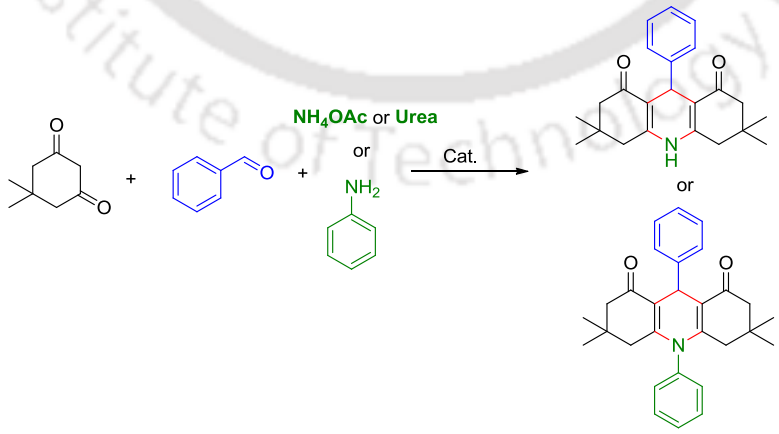
observed that the reaction of primary alcohols with ammonia is faster to afford the *N*-substituted pyrroles. Increasing the amount of primary alcohol with respect to 1,4-diol derivative increases the concentration of the primary amine and favors its attack to form the desired *N*-substituted pyrrole product (Scheme **3.4**).

Recently, the one-pot synthesis of 2-aminoquinoline and its successive *N*-alkylation with alcohols has also been described. [9g-k]



Scheme 3.5: *N*-alkylated 2-aminoquinoline synthesis *via* ADMCR

Previously, synthesis of 1,8-dioxodecahydroacridines *via* MCRs was achieved using aldehydes, dimedone, and different nitrogen sources, including urea, ammonium acetate, aniline or methyl amine using acid or heterogeneous catalyst or ionic liquids[10] (Scheme **3.6**).



Scheme 3.6: Conventional approach to the synthesis of activities1,8-dioxodecahydroacridines

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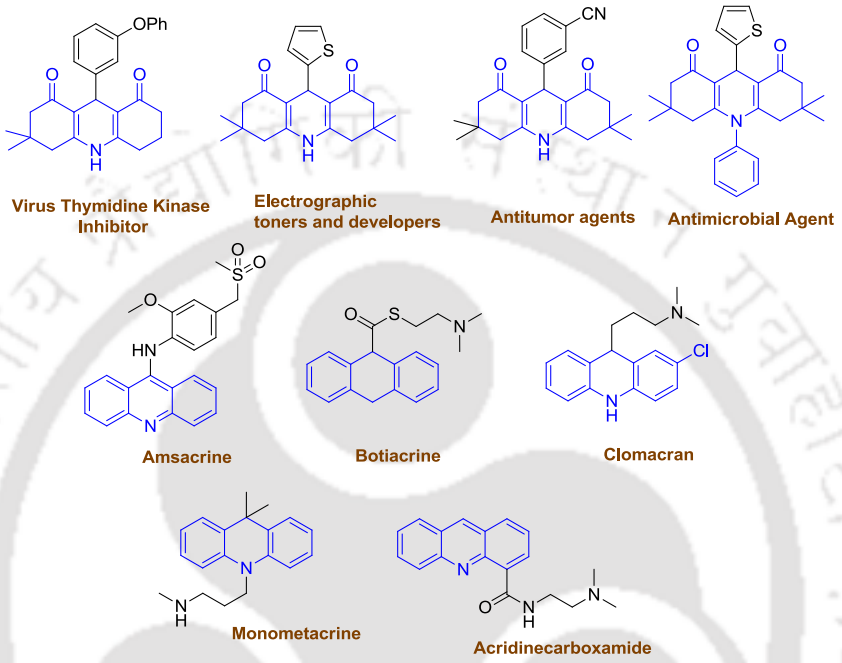
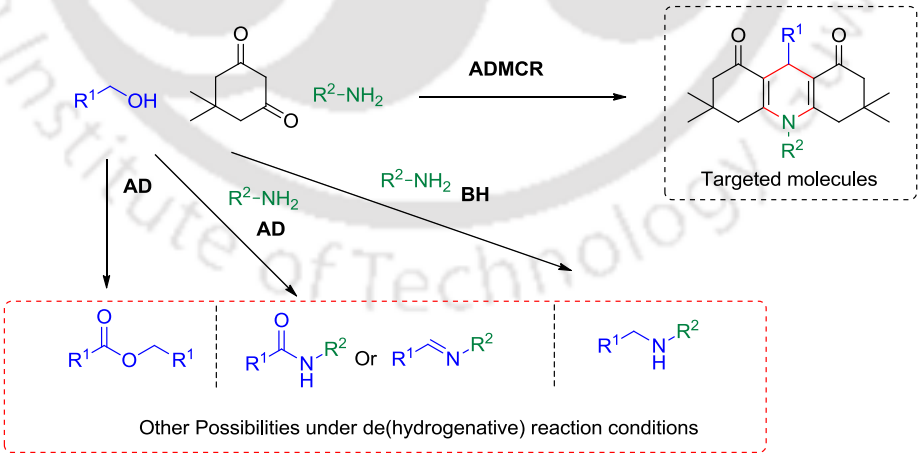
1,8-Dioxodecahydroacridines are known for their wide spectrum of biological activities (Scheme **3.7**) such as antitumor[11a], anticancer[11b], cytotoxic[11c], anti-fungal[11d], antimicrobial[11e], antimalarial[11f] and GCN5 inhibitor[11g].



Scheme 3.7: Biological active1,8-dioxodecahydroacridines derivatives



Scheme 3.8: Synthesis of the targeted molecule by suppressing the side products

Thus, it was envisioned that the synthesis of 1,8-dioxodecahydroacridines directly from renewable alcohols *via* ADMCR approach would be advantageous over the conventional

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approach. The most challenging task in the proposed ADMCR approach is the fine tuning of the reaction parameters to synthesize the targeted molecule by suppressing the side product formation as there could be many other possibilities under de(hydrogenative) reaction condition (Scheme **3.8**).

3.2. Present Work:

Herein, a Ru-Catalysed[12] ADMCR approach was utilized to synthesize 1,8-dioxodecahydroacridines. This reaction offered a cost-effective and operational simple strategy to synthesize biologically active 1,8-Dioxodecahydroacridines derivatives. The protocol offers a wide range of substrate scope and various functional groups are well-tolerated under the reaction condition.

3.2.1. Optimization of reaction conditions:

In the initial experiment, dimedone, benzyl alcohol and 4-methoxyaniline were taken as model substrates. When dimedone (1 mmol), benzyl alcohol (1.5 mmol) and 4-methoxyaniline (0.5 mmol) were heated at 135 °C in ^{t}amylalcohol for 36 h under argon in the presence of 1 mol% catalyst **2.1A** and 25 mol% ^{t}BuOK, 15% 10-(4-methoxyphenyl)-3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (**3.7a**) was obtained (Table **3.1**, entry **1**). In toluene, the yield was not improved further (Table **3.1**, entry **2**). Interestingly, under the neat condition the yield of **3.7a** was increased to 50% (Table **3.1**, entry **3**). For further enhancement of the yield of **3.7a**, alcohol amount was increased to 3 mmol, which gave **3.7a** in 60% yield after 24 h (Table **3.1**, entry **4**). With increasing time to 36 h, the yield of the desired product was further improved to 75% (Table **3.1**, entry **5**). Further increase of reaction time to 48 h or the alcohol amount did not enhance the product yield (Table **3.1**, entries **6** and **7**). Bases like ^{t}BuONa, KOH and K_2CO_3 gave moderate yield compare to ^{t}BuOK (Table **3.1**, entries **8**-**10**). Reaction at 110 °C keeping other reaction conditions same, furnishes lower yield (68%) (Table **3.1**, entry **11**). Lowering the catalyst loading to 0.5 mol% gave moderated yield (50%) after 36 h (Table **3.1**, entry **12**). Cat **2.2A** and cat **2.3A** gave inferior result under similar conditions (Table **3.1**, entries **13** and **14**).

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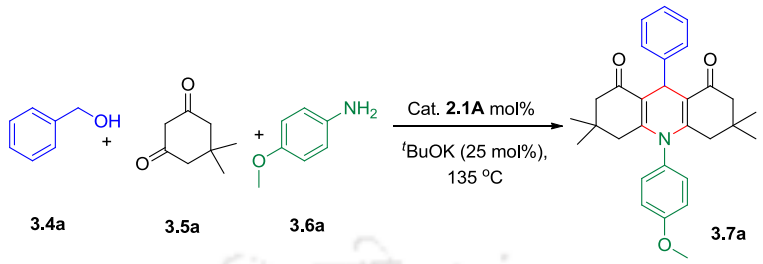
Table 3.1: Optimization of the reaction conditions for the synthesis of hexahydroacridine-1,8-dione.[a]



3.4a 3.5a 3.6a 3.7a

Entry	3.4a (mmol)	3.5a (mmol)	3.6a (mmol)	Time (h)	Solvent (mL)	Base	3.7a[b]
1	1.5	1	0.5	36	^{t}amyl alcohol	^{t}BuOK	15
2	1.5	1	0.5	36	Toluene	^{t}BuOK	13
3	1.5	1	0.5	36	Neat	^{t}BuOK	50
4	3	1	0.5	24	Neat	^{t}BuOK	60
5	**3**	**1**	**0.5**	**36**	**Neat**	**^{t}BuOK**	**75**
6	3	1	0.5	48	Neat	^{t}BuOK	76
7	5	1	0.5	36	Neat	^{t}BuOK	74
8	3	1	0.5	36	Neat	^{t}BuONa	35
9	3	1	0.5	36	Neat	KOH	33
10	3	1	0.5	36	Neat	K_2CO_3	20
11[c]	3	1	0.5	36	Neat	^{t}BuOK	68
12[d]	3	1	0.5	36	Neat	^{t}BuOK	50
13[e]	3	1	0.5	36	Neat	^{t}BuOK	30
14[f]	3	1	0.5	36	Neat	^{t}BuOK	35

[a]Reaction condition: **3.4a** (1.5-3.0 mmol), **3.5a** (1 mmol), **3.6a** (0.5 mmol), ^{t}BuOK (25 mol%), Cat **2.1A** (1 mol%), 135 °C. [b] Isolated yield. [c] 110 °C, [d] Cat **2.1A** (0.5 mol%), [e] Cat **2.2A**, [f] Cat **2.3A**.

3.2.2. Substrate scope acridine-1,8-dione derivatives:

Next, the scope and limitations of the developed protocol have been investigated. To demonstrate the practical applicability, the scope of various alcohols, amines and 1,3-diketones were investigated. The reaction of dimedone and aniline with benzyl alcohols

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containing electron-donating or electron-withdrawing functional groups at various positions efficiently produced the corresponding acridine-1,8-diones derivatives (**3.7a**-**3.7h**) (Scheme **3.9**) in good to excellent yield (70-77%). Piperonyl alcohol was responded well to afford good yield (68%) of the desired product (**3.7h**). Next, anilines with different electron-donating or electron-withdrawing functional groups were reacted with various alcohols. Reaction with *p*-Anisidine, *p*-toluidine and 4-bromoaniline afforded good yield of **3.7i**-**3.7l**. Using hetero-aromatic alcohol such as 2-thiophene methanol as substrate, compound **3.7m** was isolated in 61% yield. Compound **3.7n** has antimicrobial property[13], which can be easily prepared by this methodology with good yield (66%). 2-Pyridine methanol and 2-aminopyridine also under the optimized reaction condition gave the desired product **3.7o** and **3.7p** in good to moderate yields. Sensitive functional group like cyano (-CN) was also well survived under the reaction condition and afforded good yield of the desired product **3.7r**-**3.7s**. When, methyl 4-aminobenzoate was reacted with dimedone and alcohol, the expected product **3.7t** was not observed, instead **3.7u** was formed *via* trans-esterification.[14] Not only aniline derivative but also benzylamine reacted smoothly to give the corresponding product **3.7v** in good yield 70%. **3.7v** can be easily converted to the corresponding NH-heterocycle *via* debenzylation. Of note, good selectivity existed between amine and amide functionality, when the reaction was carried out with 4-aminobenzamide exclusively the product **3.7w** was isolated. Unfortunately, ethanol and secondary alcohol were not proficient of producing the desired product (**3.7x**-**3.7z**) in this protocol. Other 1,3-diketone like cyclohexane-1,3-dione and cyclopentane-1,3-dione also responded well (**3.7aa**-**3.7ai**). When cinnamyl alcohol was reacted cyclohexane-1,3-dione and aniline, the hydrogenated product **3.7af** was isolated. Unfortunately, when acyclic diketones like acetylacetone and ethyl acetoacetate were taken as substrates, the desired heterocycle was not formed. In most cases, the known 1,8-dioxo-decahydroacridine derivatives are symmetrical. So, I have tried to synthesize unsymmetrical 1,8- dioxo-decahydroacridine derivative using this methodology. With little modification in this methodology, the synthesis of unsymmetrical 1,8-dioxo-decahydroacridine derivatives (**3.7aj**-**3.7am**) was achieved with good yield.

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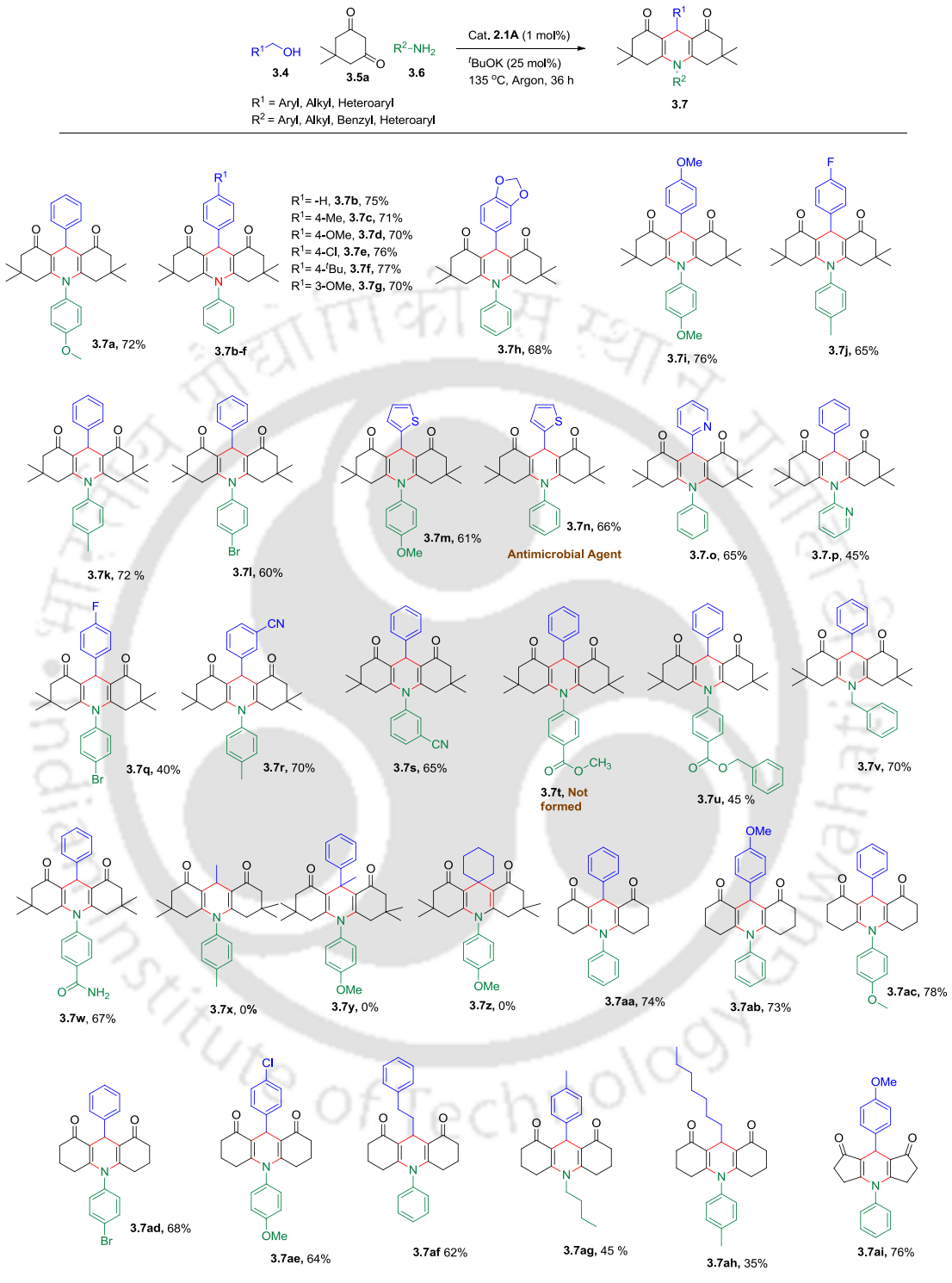

Scheme 3.9: Substrate scope for ADMCRs to synthesize *N*-substituted acridine-1,8-dione derivatives. [a]Reaction condition: **3.4** (3.0 mmol), **3.5a** (1 mmol), **3.6** (0.5 mmol), ^{t}BuOK (25 mol%), Cat **2.1A** (1 mol%), 135 °C, 36 h, Argon.

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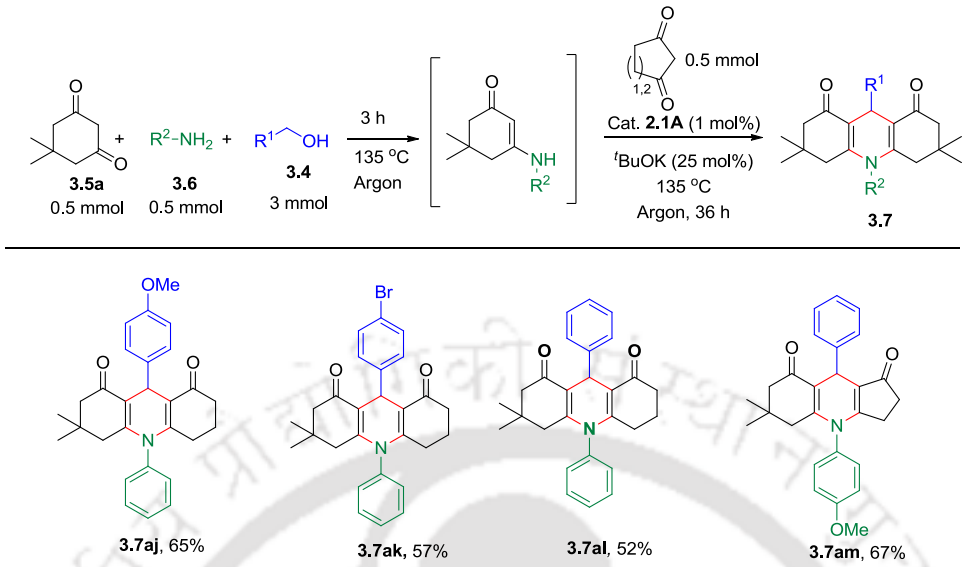
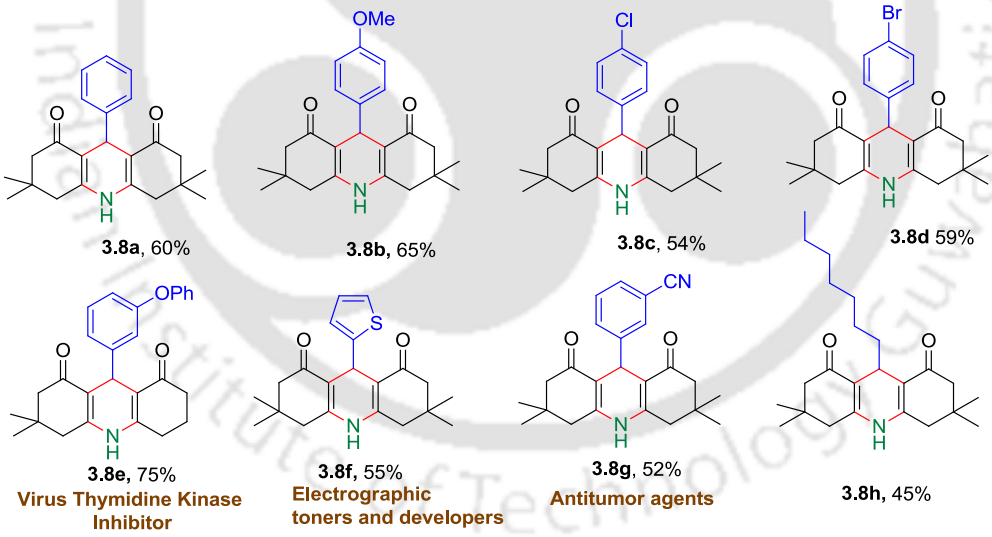


Scheme 3.10: Substrate scope for ADMCRs to synthesized unsymmetrical 1,8-dioxo-decahydroacridine derivative.[a] [a]Reaction conditions: 1,3-dione (0.5 mmol), **3.6** (0.5 mmol) and **3.4** (3.0 mmol) stirred at 135 °C for 3 h. After that added another 1,3-dione (0.5 mmol), ^{t}BuOK (25 mol%) and Cat **2.1A** (1 mol%), 135 °C, 36 h, Argon.



Scheme 3.11. Substrate scope for ADMCRs to synthesized acridine-1,8-dione derivatives with urea source.[a]

Next, urea was chosen as nitrogen source instead of aniline to synthesize NH-acridine-1,8-dione derivatives (Scheme **3.11**). An important compound **3.8e** which is used to treat infections caused by herpes simplex virus[15a] was easily prepared in good yield (75%). **3.8f** was isolated in 55% yield using hetero-aromatic alcohol such as 2-thiophene

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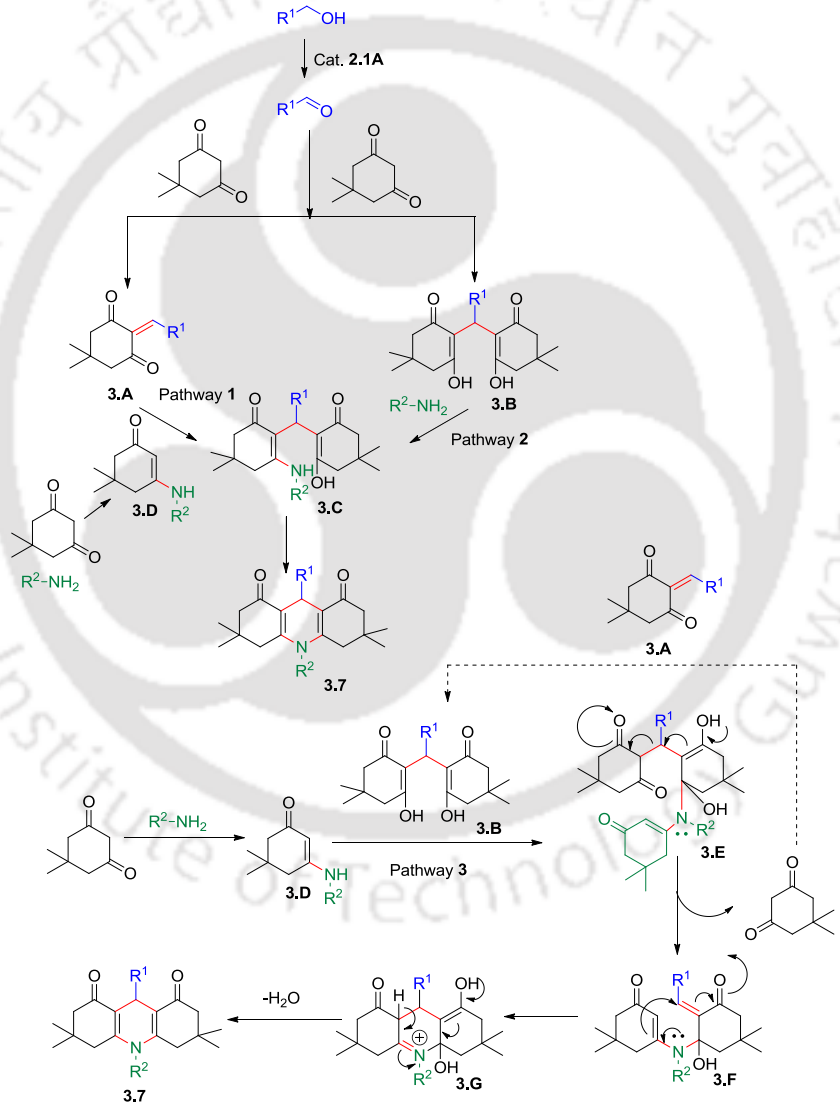
methanol as substrate. Of note, compound **3.8f** is used in electrostatographic toners and developers[15b]. This method also provides a route to synthesize compound **3.8g**, which is known to have antitumor activity.[15c] However, aliphatic alcohols such 1-octanol delivered the desired **3.8h** in 45% yield.

3.2.3. Mechanistic and kinetic investigation:



Scheme 3.12. Proposed mechanism

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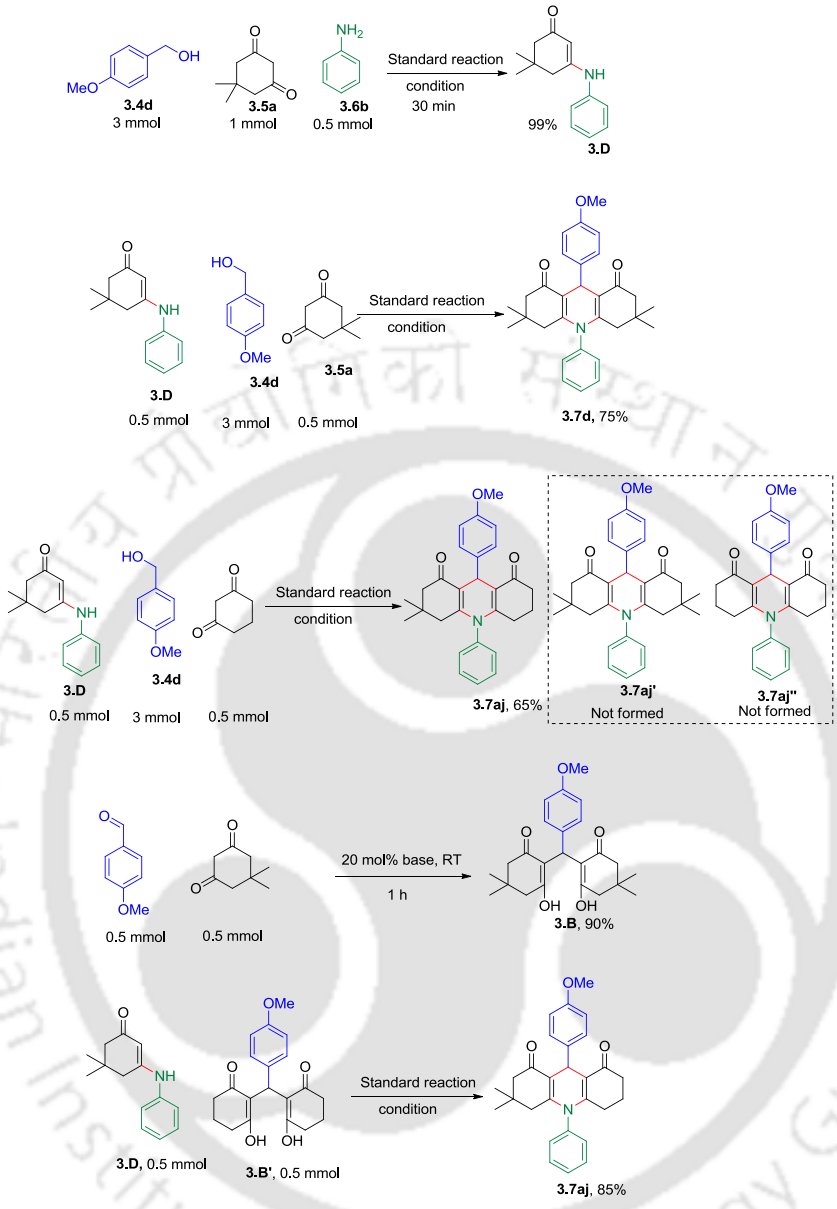

Scheme 3.13: Control experiments

Next, the mechanism of this ADMCR was proposed which is depicted in Scheme **3.12**. Two possible mechanistic pathways have been proposed. Alcohol can be dehydrogenated by Ru-catalyst and the formed aldehyde reacts with dimedone to form Knoevenagel adducts **3.A** (Pathway **1**) or intermediate **3.B**. Desired product **3.7** can be formed by the reaction of intermediate **3.B** with aniline (Pathway **2**). Another possibility is the quick formation of *β*-enaminone **3.D**, which can react with intermediate **3.A** (Pathway **1**) and **3.B** and furnished desired product **3.7** (Pathway **3**).

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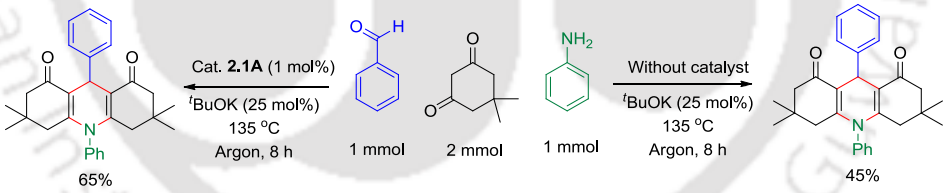
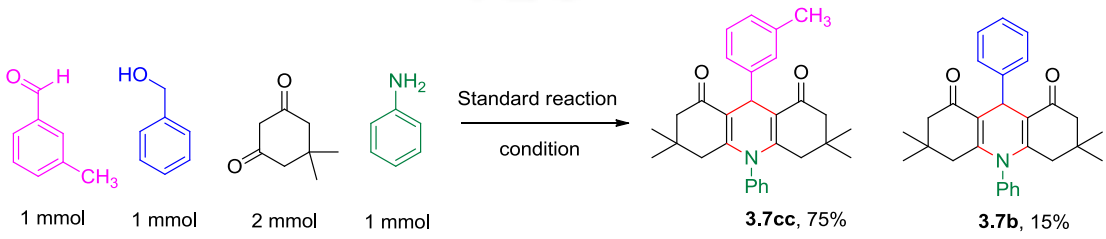
To prove the favourable pathway, some controlled experiments have been conducted (Scheme **3.13**). When, the reaction of aniline, dimedone and 4-methoxybenzyl alcohol was stopped after 30 min, *β*-enaminone **3.D** was found in quantitative yield. The reaction of *β*-enaminone **3.D**, with 4-meyhoxybenzylalcohol and dimedone afforded desired product **3.7d** with 75% isolated yield. This proves the *β*-enaminone is one of the intermediates in this reaction mixture. Same reaction with 1,3-cyclohexanedione afforded only product **3.7aj** with 65% isolated yield, no **3.7aj′** **3.7aj″** were obtained which indicates that the *β*-enaminone formation is not reversible in nature. The reaction of dimedone and aldehyde was found to be very fast even at room temperature and intermediate **3.B** is formed quantitatively within 1h. So, the possible pathway **1** and **2** was discarded. When *β*-enaminone **3.D** was reacted with intermediate **3.B′** under standard reaction condition desired product **3.7aj** was isolated in 85% yield. This indicates that pathway **3** is the most possible route of this ADMCR process.

The synthesis of 1,8-dioxo-decahydroacridine derivatives from aldehyde, dimedone and aniline is slightly accelerated by the involvement of Ru catalyst (cat **2.1A**) (Scheme **3.14**).



Scheme 3.14: The synthesis of 1,8-dioxo-decahydroacridine derivatives from aldehyde



Scheme 3.15: Competitive experiments with aldehyde and alcohol.

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To prove the dehydrogenation step is slower, further the competitive experiments have been studied. When an equimolar mixture of 3-methyl benzaldehyde and benzyl alcohol was reacted with dimedone and aniline under the standard reaction condition, product 75% **3.7cc** was formed whereas only 15% **3.7b** was formed (Scheme **3.15**).

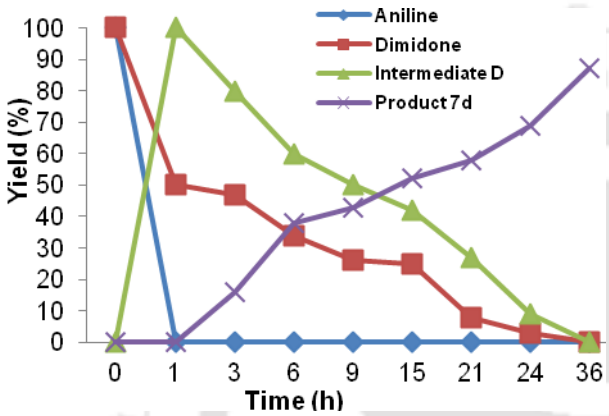

Figure 3.1. Kinetic profile of the ADMCR between 4-methoxybenzyl alcohol, dimedone and aniline. (The yield of the product was determined by NMR using CH_3CN as internal standard)

Next, the time dependent product distribution of the acceptorless dehydrogenative multicomponent reaction (ADMCR) of dimedone, aniline and 4-methoxybenzylalcohol has been studied (Figure **3.1**). During the study of the kinetic profile of this reaction, it was observed that the reaction between dimedone and aniline is much faster compared to the dehydrogenative conversion[12] of alcohol to aldehyde. First, 0.5 mmol dimedone was consumed by the 0.5 mmol of aniline to form **3.D** within 1 h. After 6 h, almost 40% product **3.7d** formation was observed and then the concentration of was **3.7d** gradually increased with time. During the kinetic study, aldehyde formation was observed. At any given time the concentration of the formed aldehyde was very less in the reaction mixture, which underpins the rapid consumption of the formed aldehyde by dimedone to form **3.B** that eventually transform to the final product **3.7**. Of note, it was observed that when the reaction is started with an aldehyde (instead of alcohol); aldehyde rapidly reacts with dimedone to form **3.B** and which reacts with aniline to form the product. Whereas, when the reaction is performed with the alcohol, before the formation of an aldehyde all the anilines converted to **3.D** and it starts reacting with **3.B** as soon as it is formed by the reaction of in situ formed aldehyde and dimedone (Scheme **3.16**).

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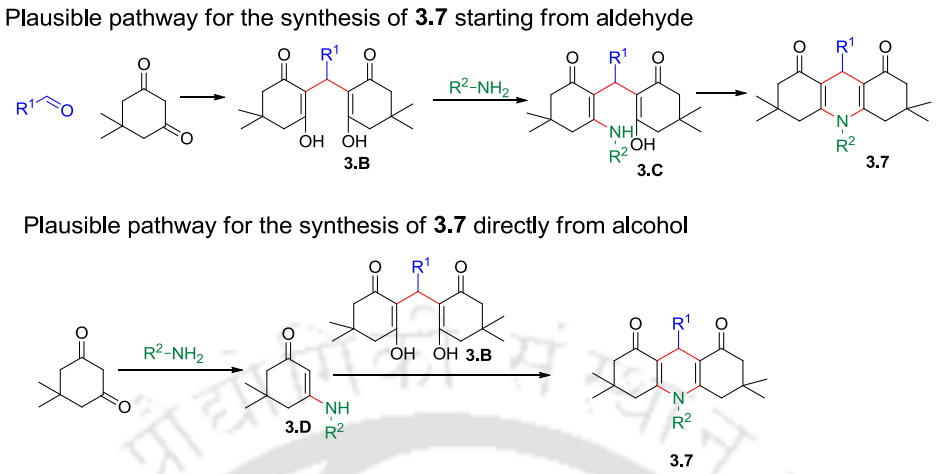
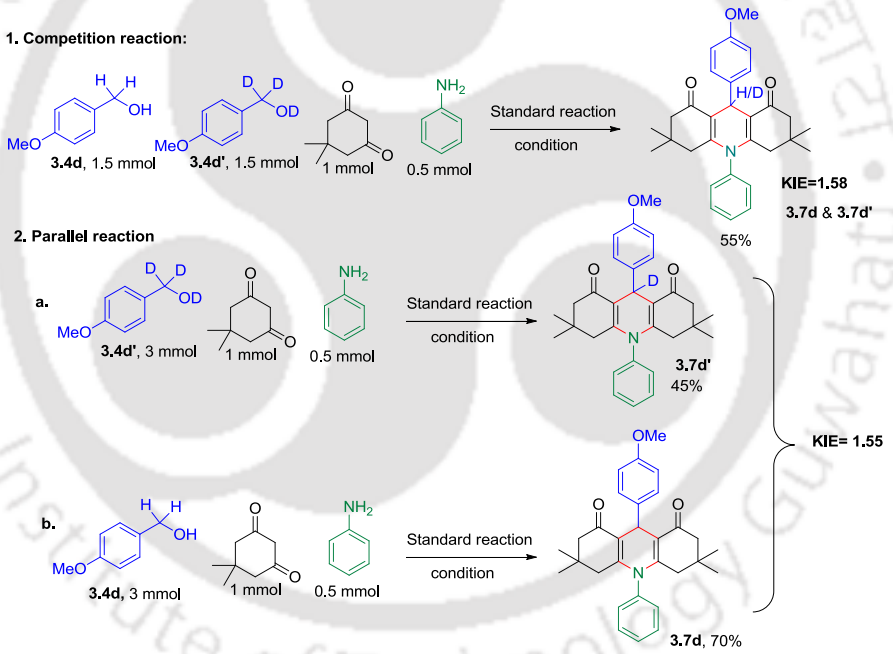
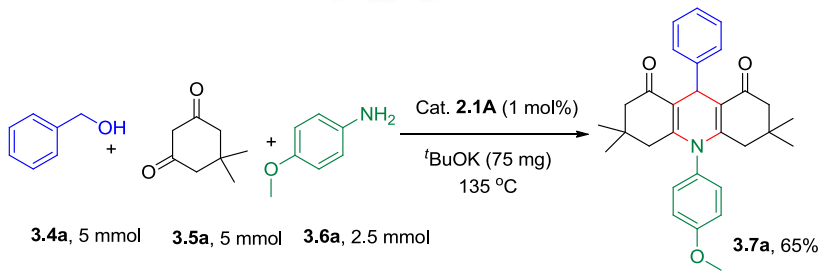


Scheme 3.16: Plausible pathways for synthesis of **3.7** from aldehyde and alcohol



Scheme 3.17: Labeling experiments



Scheme 3.18: Gram scale synthesis

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In order to gain insight, kinetic isotope experiments (KIE) were carried out (Scheme **3.17**). First, a mixture of **3.4d**/**3.4d'** (1:1, v:v) was used in a competitive experiment. The observed product ratio of the deuterated (**3.7d'**) and non-deuterated products (**3.7d**) was determined by ^{1}H NMR which indicates the KIE value ~1.58. Further, the parallel reaction with **3.4d** and **3.4d'** afforded nondeuterated and deuterated product in 70% and 45% yield respectively. The calculated k_H/k_D value (~1.55) are in close agreement with the result from the competitive reaction. This is indicative of the involvement of the C-H bond cleavage in the rate-determining step. To demonstrate the utility of this reaction the reaction was also scaled up to afford **3.7a** (0.690 g) in 65% yield (Scheme **3.18**).

3.4. Conclusion:

In conclusion, acceptorless dehydrogenative multicomponent reaction (ADMCR) was developed to synthesize 1,8-dioxo-decahydroacridine derivatives. A broad range of alcohols and amines bearing diverse functional groups were tolerated. The synthesis of various biologically important medicinal compounds was also demonstrated. In addition, mechanistic and kinetic studies were executed to understand the reaction sequences to achieve the targeted product. The slow dehydrogenation of alcohol is the key factor, which controls the reaction path. This indicates involvement of *β*-enaminone intermediate in the process. The deuterium labeling experiment underpins involvement of the α-C-H bond cleavage of the alcohol in rate-determining step.

3.5. Experimental section:

1. General information:

Unless otherwise mentioned, all chemicals were purchase from common commercial sources and used as received. $RuCl_2(PPh_3)_3$ was purchased from Sigma-Aldrich. All solvents were dried by standard procedure.[16] The catalyst preparation was carried out under argon atmosphere with freshly distilled dry THF or dichloromethane. All catalytic reactions were carried out under argon atmosphere using dry glassware and standard syringe/septa techniques. DRX-400 Varian and Bruker Avance III 600 and 400 spectrometers were used to record ^{1}H, ^{13}C NMR and ^{31}P NMR, respectively. Chemical

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shifts (δ) are reported in ppm downfield from tetramethylsilane; spin-spin coupling constants (*J*) are expressed in Hz and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, and br s = broad singlet. Column chromatography was done with SRL silica gel 100-200 mesh. Analytical thin layer chromatography (TLC) was carried out on silica gel plates (silica gel 60 F_{254}), that were visualized by exposure to ultraviolet light and an aqueous solution of *p*-anisaldehyde.

2. General procedure for the preparation of 1,8-dioxo-decahydroacridine derivatives:

Alcohol (3 mmol), dimedone (1.0 mmol) and aniline (0.5 mmol), ^{t}BuOK (25 mol%) and complex **2.1A** (1 mol%) were placed in a round bottom flask under argon atmosphere and then it was immersed in an oil bath at 135 °C and stirred at this temperature for 36 h. After that, the reaction mixture was cooled to room temperature, diluted with dichloromethane, and filtered over a plug of celite. The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (Hexane:Ethylacetate 50:50) on silica gel to afford the desired product.

3. General procedure for the preparation of unsymmetrical 1,8-dioxo-decahydroacridine derivatives:

Dimedone (0.5 mmol), aniline (0.5 mmol) and alcohol (3 mmol) was heated at 135 °C in a two necked round bottom flask under argon atmosphere for 3 h. After cooling to room temperature, 1,3-diketone (0.5 mmol), ^{t}BuOK (25 mol%) and complex **2.1A** (1 mol%) were added to it and heated at same temperature for 36 h. After that, the reaction mixture was cooled to room temperature, diluted with dichloromethane, and filtered over a plug of celite. The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (Hexane:Ethylacetate 50:50) on silica gel to afford the desired product.

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4. General procedure for the preparation of 1,8-dioxo-decahydroacridine derivatives using urea:

Alcohol (3 mmol), dimedone (1.0 mmol) and aniline (0.5 mmol), ^{t}BuOK (25 mol%) and complex **2.1A** (1 mol%) were placed in a 15 mL Ace pressure tube under argon atmosphere. The tube was sealed with screw cap and then it was immersed in an oil bath at 135 °C and stirred at this temperature for 36 h. After that, the reaction mixture was cooled to room temperature, diluted with dichloromethane, and filtered over a plug of celite. The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (Hexane:Ethylacetate 50:50) on silica gel to afford the desired product.

5. Kinetic isotope study:

Competition reaction: 4-methoxybenzyl alcohol (1.5 mmol), deuterated 4-methoxybenzyl alcohol, (1.5 mmol), dimedone (1.0 mmol) and aniline (0.5 mmol), ^{t}BuOK (25 mol%) and complex **2.1A** (1 mol%) were placed in a round bottom flask under argon atmosphere and then it was immersed in an oil bath at 135 °C and stirred at this temperature for 36 h. After that, the reaction mixture was cooled to room temperature, diluted with dichloromethane, and filtered over a plug of celite. The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (Hexane:Ethylacetate 50:50) on silica gel to afford a mixture of **3.7d** and **3.7d**' in 50% yield.

Parallel reaction: 4-methoxybenzyl alcohol (3 mmol) or deuterated 4-methoxybenzyl alcohol, (1.5 mmol), dimedone (1.0 mmol) and aniline (0.5 mmol), ^{t}BuOK (25 mol%) and complex **2.1A** (1 mol%) were placed in a round bottom flask under argon atmosphere and then it was immersed in an oil bath at 135 °C and stirred at this temperature for 36 h. After that, the reaction mixture was cooled to room temperature, diluted with dichloromethane, and filtered over a plug of celite. The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (Hexane:Ethylacetate 50:50) on silica gel to afford a mixture of **3.7d** and **3.7d**' in 70% and 45% yield respectively.

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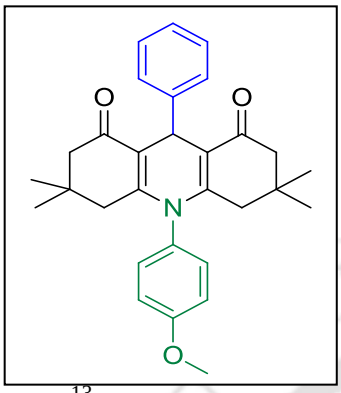
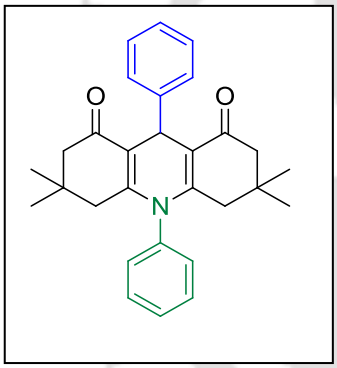
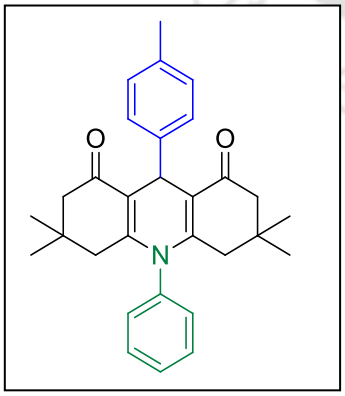
3.6. Characterization data of products



10-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7a):[17] White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.3 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 7.1 Hz, 2H), 5.26 (s, 1H), 3.90 (s, 3H), 2.14 (ABq, *J* = 21.3 Hz, 4H), 2.07 (d, *J* = 17.6 Hz, 2H), 1.84 (d, *J* = 17.5 Hz, 2H), 0.93 (s, 6H), 0.78 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.9, 159.8, 150.4, 146.3, 131.5, 131.0, 130.1, 128.1, 127.9, 125.9, 115.3, 114.9, 114.5, 55.6, 50.2, 41.8, 32.7, 32.4, 29.8, 26.8



3,3,6,6-Tetramethyl-9,10-diphenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (7b):[11b] White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57-7.54 (m, 3H), 7.43 (d, *J* = 7.3 Hz, 2H), 7.26-7.23 (m, 4H), 7.10 (t, *J* = 7.3 Hz, 1H), 5.27 (s, 1H), 2.16 (ABq, *J* = 20.4 Hz, 4H), 2.07 (d, *J* = 17.4 Hz, 2H), 1.81 (d, *J* = 17.4 Hz, 2H), 0.93 (s, 6H), 0.79 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0, 149.8, 146.2, 139.2, 129.5, 128.2, 128.0, 126.1, 114.7, 50.3, 41.9, 32.8, 32.5, 29.8, 26.9.



3,3,6,6-Tetramethyl-10-phenyl-9-(p-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7c):[18]White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58-7.51 (m, 3H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 7.2 Hz, 2H), 7.05 (d, *J* = 7.7 Hz, 2H), 5.23 (s, 1H), 2.25 (s, 3H), 2.15 (ABq, *J* = 19.9 Hz, 4H), 2.06 (d, *J* = 17.4 Hz, 2H), 1.80 (d, *J* = 17.4 Hz, 2H), 0.93 (s, 6H), 0.80 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0, 149.7, 143.4, 139.3, 135.4, 129.5, 128.9, 127.9, 114.9, 50.3, 41.9, 32.5, 32.4, 29.8, 27.0, 21.2.

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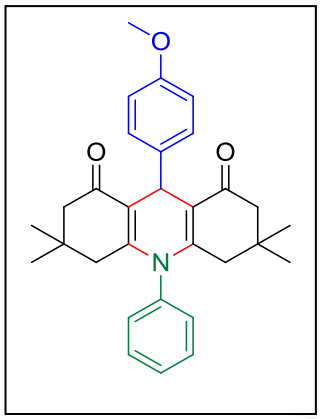
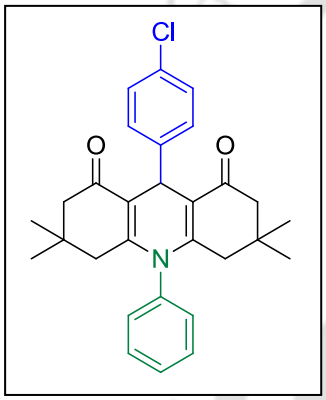
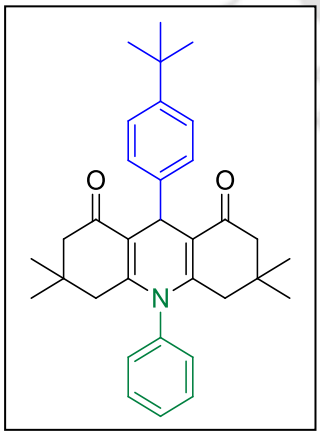


9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7d):[11b] White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 -7.50 (m, 3H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 6.9 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 5.21 (s, 1H), 3.74 (s, 3H), 2.15 (ABq, *J* = 19.9 Hz, 4H), 2.06 (d, *J* = 17.5 Hz, 2H), 1.80 (d, *J* = 17.4 Hz, 2H), 0.93 (s, 6H), 0.80 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0, 157.8, 149.6, 149.6, 139.3, 138.9, 129.5, 128.9, 114.9, 113.6, 55.2, 50.3, 41.9, 32.5, 32.0, 29.8, 26.9.



9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7e):[11b] Yellow Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59-7.53 (m, 3H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.23-7.20 (m, 4H) 5.23 (s, 1H), 2.16 (ABq, *J* = 21.33 Hz 4H), 2.06 (d, *J* = 17.5 Hz, 2H), 1.80 (d, *J* = 17.5 Hz, 2H), 0.94 (s, 6H), 0.79 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.9, 149.9, 144.9, 139.1, 131.6, 129.6, 129.4, 128.8, 128.4, 128.3, 114.4, 50.2, 41.9, 32.5, 32.5, 29.9, 26.9.



9-(4-(tert-butyl)phenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-Hexahydroacridine-1,8(2H,5H)-dione (3.7f): Off white Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61-7.51 (m, 3H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.30-7.22 (m, 4H), 5.27 (s, 1H), 2.18 (ABq, *J* = 17.9 Hz, 4H), 2.08 (d, *J* = 17.4 Hz, 2H), 1.84 (d, *J* = 17.4 Hz, 2H), 1.27 (s, 9H), 0.96 (s, 6H), 0.83 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.1, 149.6, 148.4, 143.2, 139.3, 129.4, 127.5, 125.1, 114.9, 50.4, 41.9, 34.4, 32.5, 32.2, 31.5, 29.8, 27.1. HRMS calculated for $C_{33}H_{40}NO_2$ $[M+H]^+$: 482.3059; Found: 482.3061.

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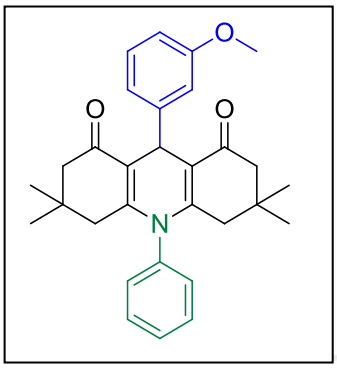
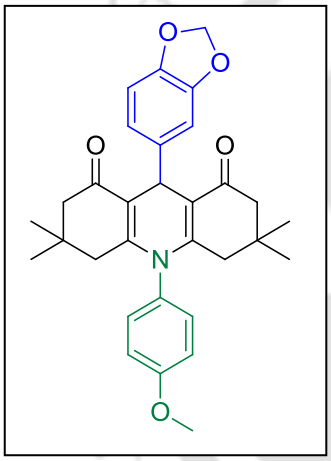


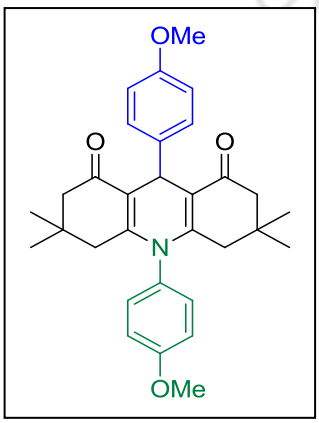
9-(3-Methoxyphenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7g):[19]

White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57-7.53 (m, 3H), 7.22 (d, *J* = 6.7 Hz, 3H), 7.14 (t, *J* = 7.8 Hz, 1H), 7.02-7.00 (m, 3H), 6.65 (dd, *J* = 7.9, 2.1 Hz, 2H), 5.26 (s, 1H), 3.78 (s, 3H), 2.16 (ABq, *J* = 17.0 Hz, 4H), 2.06 (d, *J* = 17.5 Hz, 2H), 1.81 (d, *J* = 17.5 Hz, 2H), 0.93 (s, 6H), 0.80 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 196.1, 159.4, 149.9, 147.7, 139.1, 129.5, 129.0, 120.3, 114.5, 113.6, 111.9, 55.2, 50.2, 41.9, 32.7, 32.5, 29.8, 26.9.



9-(Benzo[d][1,3]dioxol-5-yl)-10-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7h):[20]

Brown Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13-7.09 (m, 2H), 7.02 (t, *J* = 6.78 Hz, 2H), 6.93 (d, *J* = 1.7 Hz, 2H), 6.88 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.87 (s, 2H), 5.17 (s, 1H), 3.91 (s, 3H), 2.16 (ABq, *J* = 18.8 Hz, 4H), 2.05 (d, *J* = 17.5 Hz, 2H), 1.84 (dd, *J* = 17.5, 1.4 Hz, 2H), 0.94 (s, 6H), 0.82 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.1, 159.9, 150.2, 147.4, 145.7, 140.8, 131.1, 130.2, 130.2, 121.0, 115.3, 115.1, 114.8, 108.8, 108.0, 100.7, 55.7, 50.3, 41.9, 32.5, 32.5, 29.8, 27.0.



9,10-Bis(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7i):[17]

White Solid. ^{1}H NMR (600 MHz, $CDCl_3$)δ 7.33 (d, *J* = 8.6 Hz, 2H), 7.11 (t, *J* = 9.5 Hz, 2H), 7.03 (t, *J* = 7.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 5.20 (s, 1H), 3.91 (s, 2H), 3.74 (s, 3H), 2.15 ((ABq, *J* = 19.4 Hz, 4H), 2.05 (d, *J* = 17.0 Hz, 2H), 1.84 (d, *J* = 17.5 Hz, 2H), 0.94 (s, 6H), 0.80 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.1, 159.8, 157.7, 150.1, 138.9, 131.1,

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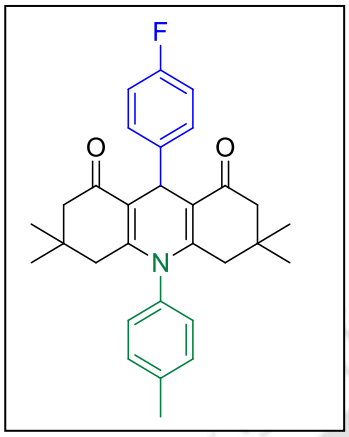
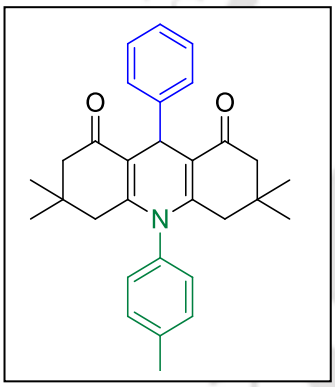
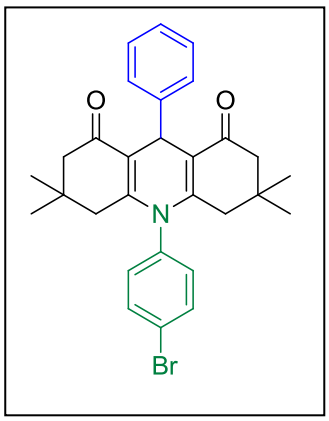
130.2, 130.2, 128.9, 115.3, 114.9, 114.9, 113.5, 55.7, 55.2, 50.3, 41.9, 32.5, 31.9, 29.9, 26.9.



9-(4-Fluorophenyl)-3,3,6,6-tetramethyl-10-(p-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7j):[19] White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40-7.35 (m, 2H), 7.33 (d, *J* = 7.7 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 2H), 6.91 (t, *J* = 8.6 Hz, 2H), 5.23 (s, 1H), 2.47 (s, 3H), 2.14 (ABq, *J* = 21.8 Hz, 4H), 2.06 (d, *J* = 17.5 Hz, 2H), 1.82 (d, *J* = 17.5 Hz, 3H), 0.93 (s, 6H), 0.78 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0, 161.2 (d, *J* = 243.2 Hz), 150.2, 142.3 (d, *J* = 3.1 Hz), 139.7, 136.3, 130.8 (d, *J* = 66.2 Hz), 129.4 (d, *J* = 8.0 Hz), 114.8 (d, *J* = 21.2 Hz), 114.5, 50.3, 41.8, 32.5, 32.2, 29.8, 26.8, 21.4.



3,3,6,6-Tetramethyl-9-phenyl-10-(p-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (7k):[11b] White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.3 Hz, 2H), 7.33 (d, *J* = 7.7 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 3H), 5.26 (s, 1H), 2.48 (s, 3H), 2.15 (ABq, *J* = 20.5 Hz, 4H), 2.06 (d, *J* = 17.5 Hz, 2H), 1.83 (d, *J* = 17.4 Hz, 2H), 0.94 (s, 6H), 0.79 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0, 150.1, 146.3, 139.6, 136.5, 128.2, 128.0, 126.0, 114.7, 50.3, 41.9, 32.8, 32.5, 29.8, 26.9, 21.



10-(4-Bromophenyl)-3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7l):[11b] White Solid. ^{1}H NMR (600 MHz, $CDCl_3$)δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 7.3 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 2H), 7.13 (d, *J* = 6.8 Hz, 2H), 7.10 (t, *J* = 6.8 Hz, 1H), 5.26 (s, 1H), 2.16 (ABq, *J* = 20.6 Hz, 4H), 2.05 (d, *J* = 17.4 Hz, 2H), 1.81 (d, *J* = 17.3 Hz, 0H), 0.95 (s, 6H), 0.80 (s, 6H). ^{13}C NMR

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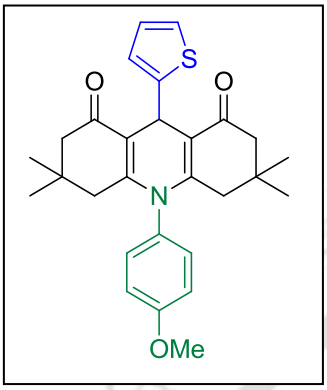
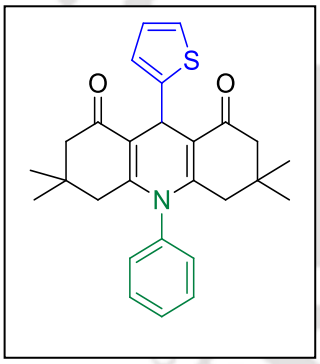
(150 MHz, $CDCl_3$) δ 195.9, 149.3, 149.3, 146.0, 138.3, 133.6, 131.3, 128.2, 127.9, 126.2, 123.6, 115.0, 50.2, 42.0, 32.6, 29.8, 26.9.



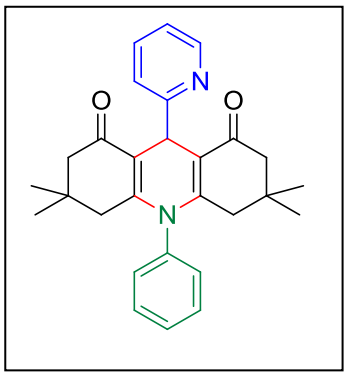
10-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-9-(thiophen-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7m):[21]

Yellow Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 (d, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 7.1 Hz, 1H), 7.01-6.98 (m, 4H), 6.83 (t, *J* = 5.0 Hz, 1H), 5.64 (s, 1H), 3.89 (s, 3H), 2.16 (ABq, *J* = 12.1 Hz, 4H), 2.08 (d, *J* = 17.6 Hz, 2H), 1.83 (d, *J* = 17.5 Hz, 2H), 0.94 (s, 6H), 0.85 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.8, 159.9, 150.7, 150.5, 131.4, 130.9, 130.5, 127.0, 124.1, 122.4, 115.4, 114.8, 114.1, 55.7, 50.3, 41.7, 32.4, 30.0, 27.3, 26.8. HRMS calculated for $C_{28}H_{32}NO_3S$ $[M+H]^+$: 462.2103; Found 462.2103.



3,3,6,6-Tetramethyl-10-phenyl-9-(thiophen-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7n):[13]

Yellow Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59-7.47 (m, 3H), 7.31-7.20 (m, 2H),7.04-6.98 (m, 2H), 6.85 (dd, *J* = 5.1, 3.5 Hz, 1H), 5.66 (s, 1H), 2.15 (ABq, *J* = 11.7 Hz,, 5H), 2.09 (d, *J* = 17.5 Hz, 2H), 1.79 (d, *J* = 17.5 Hz, 2H), 0.95 (s, 6H), 0.85 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.8, 150.4, 150.2, 139.0, 130.6, 130.1, 129.7, 129.5, 127.1, 124.2, 122.5, 114.2, 50.3, 41.8, 32.5, 30.0, 27.4, 26.8.



3,3,6,6-Tetramethyl-10-phenyl-9-(pyridin-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7o):[13]

Yellow Solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 4.0 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.53-7.50 (m, 5H), 6.98 (t, *J* = 5.4 Hz, 1H), 5.38 (s, 1H), 2.21 (d, *J* = 16.1 Hz, 2H), 2.14-2.03 (m, 4H), 1.83 (d, *J* = 17.3 Hz, 2H), 0.94 (s, 6H), 0.78 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ

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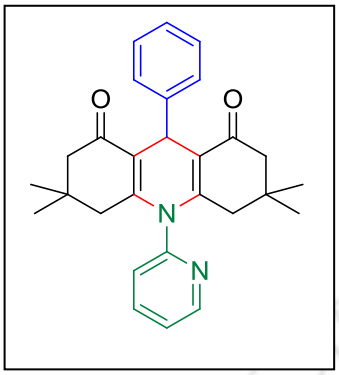
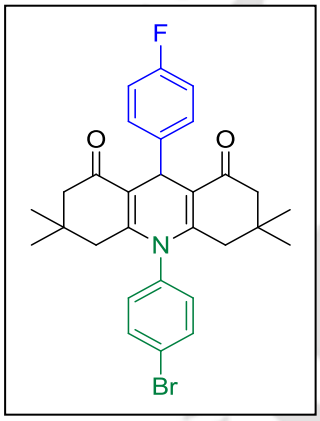
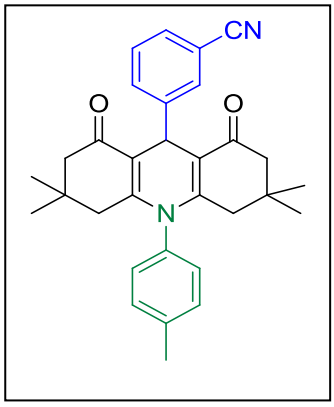
196.2, 163.4, 151.4, 149.2, 140.0, 135.6, 130.1, 129.2, 123.7, 121.2, 113.9, 50.4, 41.8, 35.20, 32.7, 29.8, 26.7.



3,3,6,6-Tetramethyl-9-phenyl-10-(pyridin-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7p):[11d] Yellow Solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.95 (t, *J* = 7.5 Hz, 1H), 7.55-7.42 (m, 2H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.26-7.22 (m, 3H), 7.09 (t, *J* = 7.2 Hz, 1H), 5.27 (s, 1H), 2.26-2.09 (m, 6H), 1.71 (d, *J* = 17.3 Hz, 2H), 0.94 (s, 6H), 0.81 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 195.8, 152.7, 150.4, 149.0, 146.2, 139.1, 128.2, 128.2, 126.1, 124.8, 124.6, 115.1, 50.4, 41.5, 33.1, 32.6, 29.8, 27.1.



10-(4-Bromophenyl)-9-(4-fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7q): White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.36 (t, *J* = 6.8 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.92 (t, *J* = 8.5 Hz, 2H), 5.23 (s, 1H), 2.16 (ABq, *J* = 20.9 Hz, 4H), 2.05 (d, *J* = 17.4 Hz, 2H), 1.81 (d, *J* = 17.4 Hz, 2H), 0.96 (s, 6H), 0.81 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.9, 161.3 (d, *J* = 243.6 Hz), 149.3, 142.0 (d, *J* = 3.0 Hz), 138.1, 133.6, 129.4 (d, *J* = 8.0 Hz), 123.7, 115.0, 114.9 (d, *J* = 4.7 Hz), 50.2, 42.0, 32.6, 32.2, 29.8, 26.9. HRMS calculated for $C_{29}H_{30}BrFNO_2$ $[M+H]^+$: 522.1444, Found: 522.1439.



3-(3,3,6,6-Tetramethyl-1,8-dioxo-10-(p-tolyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridin-9-yl)benzonitrile (3.7r):

White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.7 Hz, 1H), 7.61 (s, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.38-7.32 (m, 3H), 7.13-7.05 (d, *J* = 6.7 Hz, 1H), 5.26 (s, 1H), 2.49 (s, 3H), 2.15 (ABq, *J* = 23.5 Hz, 4H), 2.06 (d, *J* = 17.6 Hz, 2H), 1.86

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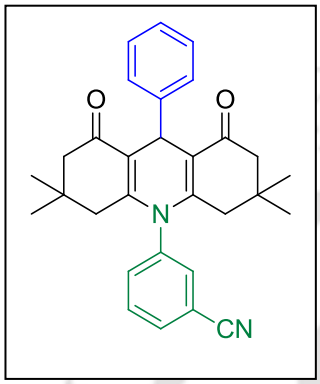
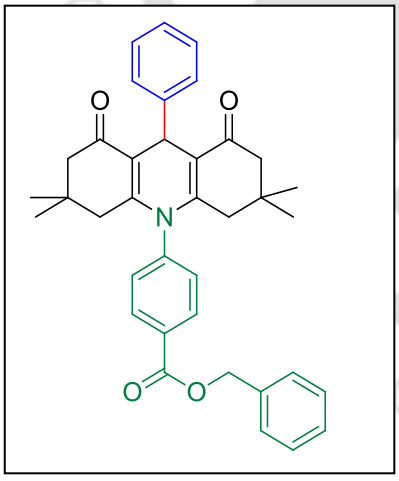
(d, *J* = 17.6 Hz, 2H), 0.95 (s, 6H), 0.79 (s, 6H). ^{13}C NMR (150MHz, $CDCl_3$) δ 195.9, 150.7, 147.9, 139.9, 136.1, 133.6, 131.2, 130.7, 129.9, 129.6, 128.9, 119.7, 113.8, 112.0, 50.2, 41.9, 33.3, 32.5, 29.7, 26.9, 21.4. HRMS calculated for $C_{31}H_{33}N_2O_2$ $[M+H]^+$: 465.2542; Found 465.2541.



3-(3,3,6,6-Tetramethyl-1,8-dioxo-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzonitrile (3.7s):

White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.8 Hz, 1H), 7.76 (t, *J* = 7.9 Hz, 1H), 7.60 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.30-7.26 (m, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 5.29 (s, 1H), 2.20 (ABq, *J* = 17.4 Hz, 4H), 2.05 (d, *J* = 17.4 Hz, 2H), 1.75 (d, *J* = 17.2 Hz, 2H), 0.99 (s, 6H), 0.84 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.8, 148.5, 145.6, 140.3, 133.2, 128.4, 127.9, 126.4, 117.4, 115.4, 50.2, 42.1, 32.7, 32.7, 29.8, 27.0. HRMS calculated for $C_{30}H_{31}N_2O_2$ $[M+H]^+$: 451.2386; Found: 451.2385.



Benzyl-4-(3,3,6,6-tetramethyl-1,8-dioxo-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzoate (3.7u):

White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 7.1 Hz, 2H), 7.47-7.41 (m, 4H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.30-7.24 (m, 3H), 7.13 (t, *J* = 7.4 Hz, 1H), 5.45 (s, 2H), 5.30 (s, 1H), 2.19 (ABq, *J* = 18.4 Hz, 4H), 2.07 (d, *J* = 17.4 Hz, 2H), 1.80 (d, *J* = 17.3 Hz, 2H), 0.96 (s, 6H), 0.81 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 195.8, 165.3, 148.9, 146.0, 143.4, 135.6, 131.3, 128.9, 128.8, 128.7, 128.3, 128.0, 126.2, 115.1, 77.3, 77.1, 76.9, 50.3, 42.0, 32.8, 32.6, 29.8, 26.9. HRMS calculated for $C_{37}H_{38}NO_4$ $[M+H]^+$: 560.2801; Found: 560.2803.

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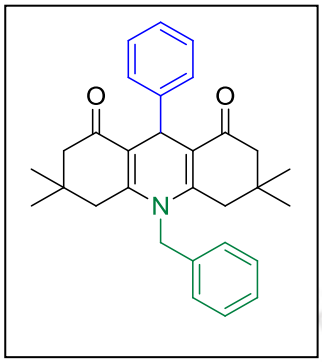
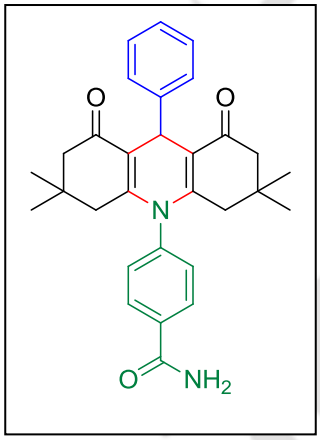
10-Benzyl-3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7v):[22]

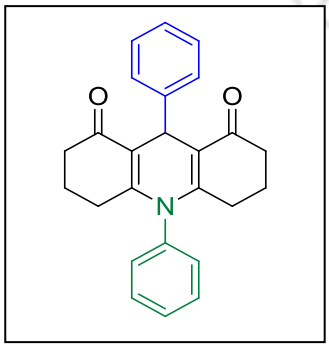


White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (t, *J* = 7.4 Hz, 2H), 7.34 (d, *J* = 7.1 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.21-7.13 (m, 4H), 7.08 (d, *J* = 7.2 Hz, 1H), 5.34 (s, 1H), 4.90 (s, 2H), 2.49 (d, *J* = 16.6 Hz, 2H), 2.30 (d, *J* = 16.6 Hz, 2H), 2.19 (ABq, *J* = 9.5 Hz, 4H), 0.98 (s, 6H), 0.88 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.8, 150.7, 150.7, 145.9, 137.2, 129.3, 128.0, 128.0, 126.0, 125.5, 115.4, 50.1, 48.8, 40.28, 32.8, 32.2, 28.5, 28.3.



4-(3,3,6,6-Tetramethyl-1,8-dioxo-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzamide (3.7w):

White Solid. ^{1}H NMR (600 MHz, $CDCl_3$)δ 8.04 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 7.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 7.7 Hz, 2H), 7.11 (t, *J* = 7.3 Hz, 1H), 5.28 (s, 1H), 2.17 (ABq, *J* = 20.0 Hz, 4H), 2.06 (d, *J* = 17.5 Hz, 2H), 1.79 (d, *J* = 17.4 Hz, 2H), 0.94 (s, 6H), 0.80 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0, 168.0, 149.2, 146.0, 142.3, 134.6, 130.2, 129.4, 128.3, 127.9, 126.2, 115.0, 50.3, 42.0, 32.6, 29.8, 26.9. HRMS calculated for $C_{30}H_{33}N_2O_3$ $[M+H]^+$: 469.2491; Found: 469.2493.



9,10-Diphenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7aa):[23]

Yellow Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57-7.52 (m, 3H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.31-7.24 (m, 4H), 7.15 (t, *J* = 7.3 Hz, 1H), 5.41 (s, 1H), 2.39 (dt, *J* = 16.6, 4.6 Hz, 2H), 2.32-2.16 (m, 4H), 2.08-2.00 (m, 2H), 1.89 (dt, *J* = 13.6, 4.7 Hz, 2H), 1.82-1.77 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ

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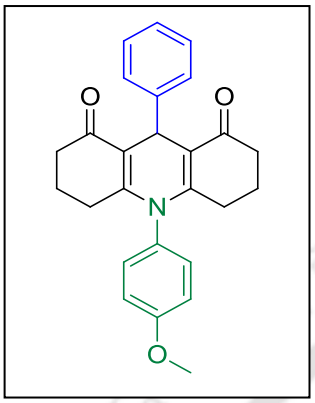
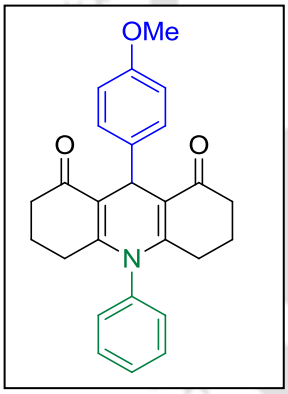
196.2, 151.6, 146.6, 139.2, 130.4, 130.0, 129.7, 129.5, 129.4, 128.3, 127.9, 126.1, 115.6, 36.9, 32.1, 28.4, 21.2.



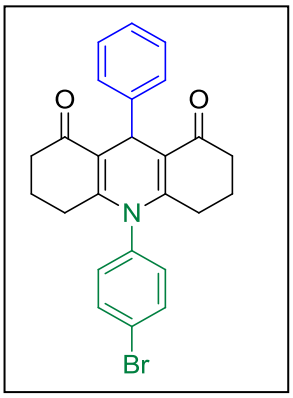
10-(4-Methoxyphenyl)-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7ab):

Yellow Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 2H), 7.18-7.14 (m, 2H), 7.11 (t, *J* = 7.3 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 2H), 5.37 (s, 1H), 3.88 (s, 3H), 2.36 (dt, *J* = 16.9, 4.6 Hz, 2H), 2.28-2.14 (m, 4H), 2.06 (dt, *J* = 17.8, 4.6 Hz, 2H), 1.89-1.85 (m, 2H), 1.80-1.75 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.3, 160.0, 152.2, 146.6, 131.6, 130.9, 130.3, 128.3, 127.8, 126.1, 115.6, 115.2, 114.8, 55.7, 36.8, 32.1, 28.4, 21.2. HRMS calculated for $C_{26}H_{26}NO_3$ $[M+H]^+$: 400.1913; Found: 400.1919.



9-(4-Methoxyphenyl)-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7ac):[23]

White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 -7.43 (m, 3H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.33-7.22 (m, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.34 (s, 1H), 3.78 (s, 3H), 2.39 (dt, *J* = 16.6, 4.6 Hz, 2H), 2.32-2.15 (m, 4H), 2.04 (dt, *J* = 17.7, 4.6 Hz, 2H), 1.92-1.87 (m, 2H), 1.85-1.75 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.3, 157.9, 151.4, 139.3, 139.2, 129.4, 128.8, 115.9, 113.7, 55.3, 36.9, 31.3, 28.4, 21.2.



10-(4-Bromophenyl)-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7ad):[24]

White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 7.2 Hz, 2H), 7.26 (d, *J* = 5.9 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 5.37 (s, 1H), 2.38 (dt, *J* = 16.6, 4.6 Hz, 2H), 2.29-2.11 (m, 4H), 2.03 (dt, *J* = 17.7, 4.6 Hz, 2H), 1.93-1.87 (m, 2H), 1.83-1.74 (m, 2H). ^{13}C NMR (150

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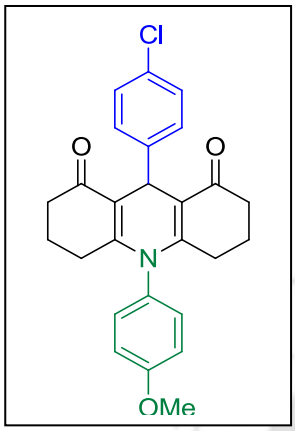
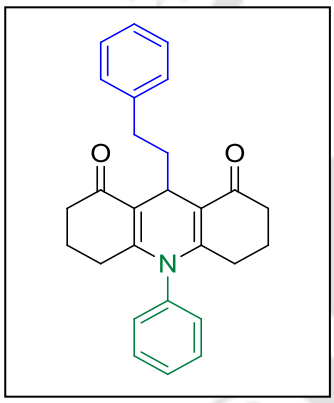
MHz, $CDCl_3$) δ 196.1, 151.0, 146.4, 138.2, 128.4, 127.8, 126.2, 123.6, 116.0, 36.8, 32.1, 28.5, 21.2. HRMS calculated for $C_{25}H_{23}BrNO_2$ $[M+H]^+$: 448.0912, Found: 448.0911.



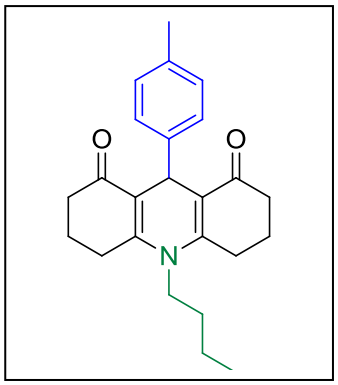
9-(4-Chlorophenyl)-10-(4-methoxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7ae): [25]

White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.17 -7.11 (m, 2H), 7.01 (d, *J* = 8.2 Hz, 2H), 5.32 (s, 1H), 3.88 (s, 3H), 2.35 (dt, *J* = 16.6, 4.6 Hz, 2H), 2.29-2.14 (m, 2H), 2.06 (dt, *J* = 17.2, 4.1 Hz, 2H), 1.91-1.87 (m, 2H), 1.82-1.71 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.3, 160.0, 152.4, 145.2, 131.7, 131.5, 130.8, 130.2, 129.3, 128.4, 115.3, 55.8, 36.8, 31.8, 28.4, 21.2



9-Phenethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7af):

White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50-7.48 (m, 3H), 7.23 (t, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 6.6 Hz, 2H), 7.17 -7.11 (m, 3H), 4.40 (t, *J* = 5.5 Hz, 1H), 2.64-2.57 (m, 2H), 2.44 (dt, *J* = 16.5, 4.4 Hz, 2H), 2.30 -2.08 (m, 4H), 1.95 (dt, *J* = 17.6, 4.4 Hz, 2H), 1.91-1.87 (m, 2H), 1.80-1.70 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 196.7, 152.7, 143.1, 139.3, 129.4, 128.4, 128.3, 125.6, 115.0, 37.8, 37.0, 31.8, 28.4, 26.2, 21.4. HRMS calculated for $C_{27}H_{28}NO_2$ $[M+H]^+$: 398.2120; found: 398.2121.



10-Butyl-9-(p-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7ag):

White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.9 Hz, 2H), 7.00 (d, *J* = 7.7 Hz, 2H), 5.30 (s, 1H), 3.66 (t, *J* = 7.8 Hz, 2H), 2.76 (dt, *J* = 16.9, 5.1 Hz, 2H), 2.58-2.50 (m, 2H), 2.41 (dt, *J* = 16.4, 4.9 Hz, 2H), 2.33-2.27 (m, 2H), 2.25

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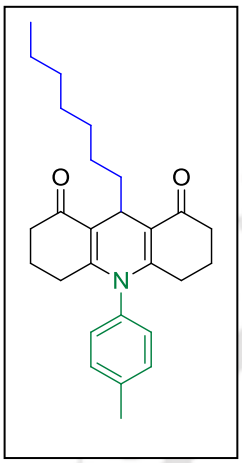
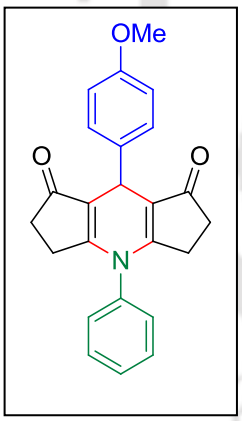
(s, 3H), 2.11-1.94 (m, 4H), 1.67-1.59 (m, 2H), 1.42-1.34 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0, 151.9, 143.3, 135.3, 128.8, 127.5, 116.6, 45.1, 36.6, 33.2, 31.1, 26.7, 21.4, 21.1, 20.0, 13.8. HRMS calculated for $C_{24}H_{30}NO_2$ $[M+H]^+$: 364.2277; Found:364.2272.



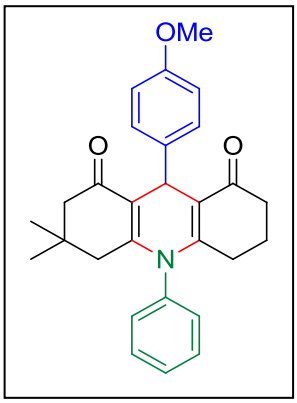
9-Heptyl-10-(p-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7ah):

White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.1 Hz, 2H), 7.05 (d, *J* = 8.9 Hz, 2H), 4.26 (s, 1H), 2.47-2.39 (m, 5H, $-CH_3$, $-CH_2-$), 2.29-2.05 (m, 4H), 1.97 (dt, *J* = 17.7, 4.5 Hz, 2H), 1.91-1.86 (m, 2H), 1.82-1.74 (m, 2H), 1.39-1.33 (m, 2H), 1.29-123 (m, 10H), 0.86 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.8, 152.8, 139.4, 136.7, 115.1, 37.1, 36.1, 32.1, 30.0, 29.6, 28.4, 26.0, 25.1, 22.8, 21.4, 21.3, 14.3. HRMS calculated for $C_{27}H_{36}NO_2$ [M+H]: 406.2746; found: 406.2745.



4,8-Diphenyl-2,3,5,6-tetrahydrodicyclopenta[b,e]pyridine-1,7(4H,8H)-dione (3.7ai):

Yellow Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57-7.53 (m, 3H), 7.36-7.33 (m, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 2H), 4.82 (s, 1H), 3.76 (s, 3H), 2.48 -2.30 (m, 8H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.1, 165.5, 158.3, 137.1, 135.8, 130.3, 130.1, 129.9, 129.1, 128.6, 128.2, 121.4, 113.8, 55.3, 34.4, 33.6, 25.0. HRMS calculated for $C_{24}H_{22}NO_3$ [M+H]: 372.1600; found: 372.1600.



9-(4-Methoxyphenyl)-3,3-dimethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7aj):[26]

White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 -7.53 (m, 3H), 7.36 (d, *J* = 8.7 Hz, 2H), 7.28-7.26 (m, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.29 (s, 1H), 2.38-2.02 (m, 7H), 1.90-1.79 (m, 3H), 0.96 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.3, 196.1, 157.8, 151.4, 149.5, 139.2, 139.0, 129.4, 128.9, 115.9, 114.9,

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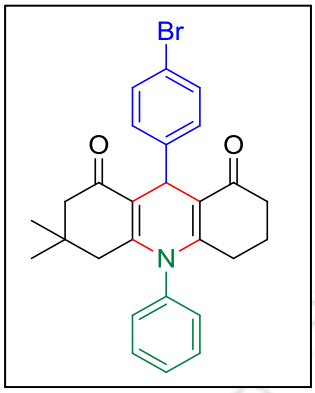
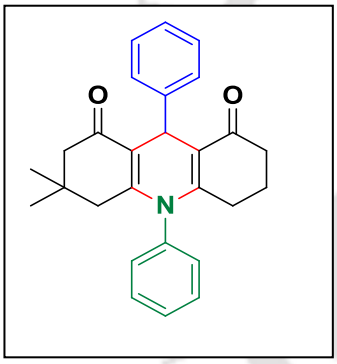
113.6, 55.2, 50.3, 41.9, 36.8, 32.5, 31.7, 29.8, 28.4, 27.0, 21.2.



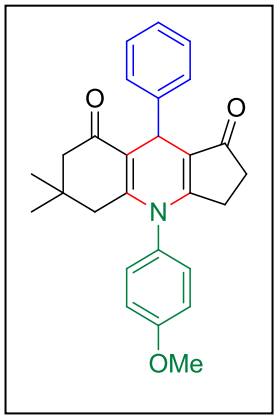
9-(4-Bromophenyl)-3,3-dimethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7ak): [26]

White Solid. ^{1}H NMR (600 MHz, , $CDCl_3$) δ 7.56 (t, *J* = 7.5 Hz, 3H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 2H), 5.30 (s, 1H), 2.42-2.00 (m, 6H), 1.96-1.78 (m, 4H), 0.97 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.1, 195.9, 151.83, 149.9, 145.6, 139.1, 131.3, 129.8, 129.6, 119.9, 115.3, 114.4, 50.3, 41.9, 36.8, 32.5, 32.3, 29.8, 28.5, 27.0, 21.3.



3,3-Dimethyl-9,10-diphenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7al):[27]

White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56-7.51 (m, 3H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.26-7.24 (m, 4H), 7.12 (t, *J* = 7.6 Hz, 1H), 5.34 (s, 1H), 2.37-2.00 (m, 8H), 1.89-1.75 (m, 2H), 0.94 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.1, 196.0, 151.6, 149.7, 146.5, 139.3, 129.5, 128.3, 127.9, 126.1, 115.7, 114.8, 50.4, 41.9, 36.9, 32.5, 32.5, 29.8, 28.5, 27.0, 21.2.



4-(4-Methoxyphenyl)-6,6-dimethyl-9-phenyl-2,3,5,6,7,9-hexahydro-1H-cyclopenta[b]quinoline-1,8(4H)-dione (3.7am):

White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 3.7 Hz, 2H), 7.26-7.18 (m, 2H), 7.15 (t, *J* = 7.0 Hz, 1H), 7.05 (t, *J* = 6.2 Hz, 2H), 5.06 (s, 1H), 3.92 (s, 2H), 2.33-2.04(m, 8H), 1.00 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.3, 195.9, 164.9, 160.1, 150.9, 145.5, 130.6, 130.10, 130.0, 128.3, 127.9, 126.4, 120.4, 115.3, 115.2, 115.1, 55.7, 50.4,

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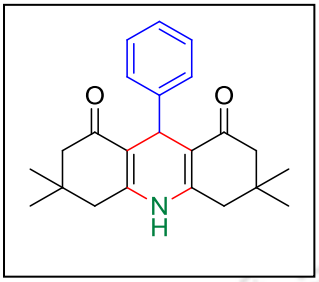
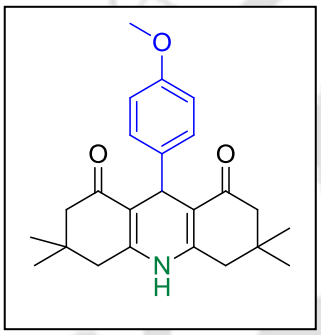
41.3, 34.3, 34.0, 32.5, 29.5, 27.3, 25.8. HRMS calculated for $C_{27}H_{28}NO_3$ $[M+H]^+$: 414.2069; Found: 414.2071.



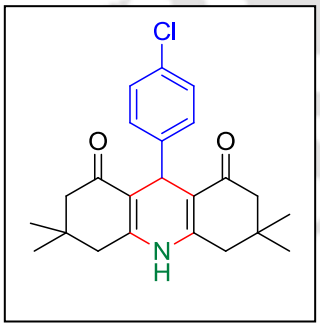
3,3,6,6-Tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.8a):[28]

White Solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.1 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 2H), 7.03 (t, *J* = 7.5 Hz, 1H), 5.06 (s, 1H), 2.36-2.00 (m, 8H), 1.04 (s, 6H), 0.93 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.4, 147.9, 146.6, 128.2, 128.1, 126.1, 113.9, 51.0, 41.3, 33.8, 32.8, 29.6, 27.3.



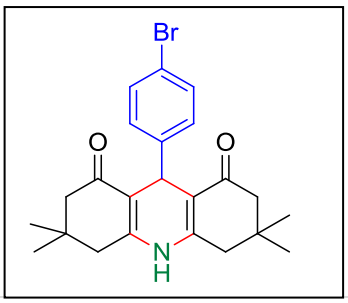
9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.8b): [28]

White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.72 (d, *J* = 8.7 Hz, 2H), 6.34 (brs, 1H), 5.02 (s, 1H), 3.70 (s, 3H), 2.33 (d, *J* = 16.6 Hz, 2H), 2.25-2.12 (m, 6H), 1.07 (s, 6H), 0.96 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.6, 157.7, 147.4, 139.0, 129.1, 114.1, 113.4, 55.2, 50.8, 41.3, 32.9, 32.8, 29.6, 27.3.



9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.8c):[28]

Yellow Solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.5 Hz, 2H), 7.15 (d, *J* = 7.5 Hz, 2H), 5.05 (s, 1H), 2.40 -2.12 (m, 8H), 1.08 (s, 6H), 0.96 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.3, 147.8, 145.1, 131.7, 129.6, 128.2, 113.6, 50.9, 41.4, 33.5, 32.8, 29.6, 27.3.



9-(4-Bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.8d):[28]

White Solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.71 (brs, 1H), 5.04 (s, 1H), 2.38-2.12 (m, 8H), 1.08 (s, 6H), 0.96 (s, 6H). ^{13}C NMR

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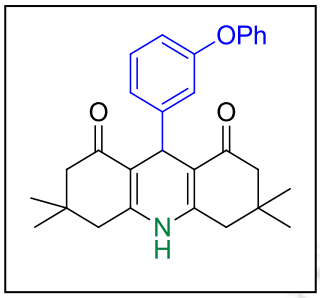
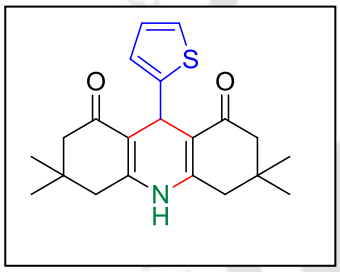
(125 MHz, $CDCl_3$) δ195.4, 148.0, 145.7, 131.1, 130.1, 119.9, 113.5, 77.4, 77.1, 76.9, 50.9, 41.3, 33.6, 32.8, 29.6, 27.3.



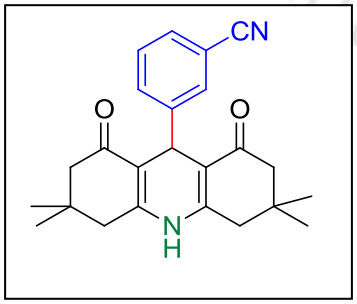
3,3,6,6-Tetramethyl-9-(3-phenoxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.8e):[15a]

Yellow Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, *J* = 7.7 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.01 (t, *J* = 7.3 Hz, 1H), 6.92 (s, 1H), 6.88 (d, *J* = 8.0 Hz, 3H), 6.77 (brs, 1H), 6.70 (d, *J* = 7.9 Hz, 1H), 5.08 (s, 1H), 2.32 (d, *J* = 16.7 Hz, 2H), 2.26 -2.10 (m, 6H), 1.06 (s, 6H), 0.94 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ ^{13}C NMR (151 MHz, $CDCl_3$) δ 195.6, 157.8, 156.8, 148.6, 148.1, 129.6, 129.2, 124.1, 122.7, 118.7, 118.4, 117.0, 113.4, 50.8, 41.1, 33.6, 32.7, 29.6, 27.2.



3,3,6,6-Tetramethyl-9-(thiophen-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.8f):[28]

White Solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.45 (s, 1H), 7.14 (d, *J* = 5.0 Hz, 1H), 6.81-6.78 (m, 1H), 6.66 (d, *J* = 3.1 Hz, 1H), 5.15 (s, 1H), 2.45 (d, *J* = 17.1 Hz, 1H), 2.33 (d, *J* = 17.1 Hz, 1H), 2.22 (d, *J* = 16.1 Hz, 1H), 2.08 (d, *J* = 16.1 Hz, 1H), 1.03 (s, 6H), 0.94 (s, 6H).^{13}C NMR (150 MHz, DMSO-d_6) δ 194.4, 151.0, 149.7, 126.2, 123.1, 122.9, 110.9, 50.2, 39.6, 32.1, 29.2, 27.3, 26.5.



3-(3,3,6,6-Tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridin-9-yl)benzonitrile (3.8g):[15c]

White Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.7 Hz, 1H), 7.51 (s, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 5.08 (s, 1H), 2.39 (d, *J* = 16.7 Hz, 2H), 2.32 -2.21 (m, 4H), 2.16 (d, *J* = 16.4 Hz, 2H), 1.09 (s, 65H), 0.96 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.2, 148.0, 147.8, 133.7, 131.4, 129.9, 128.7, 119.6, 113.1, 112.0, 50.7, 41.4, 34.0, 32.9, 29.5, 27.4.

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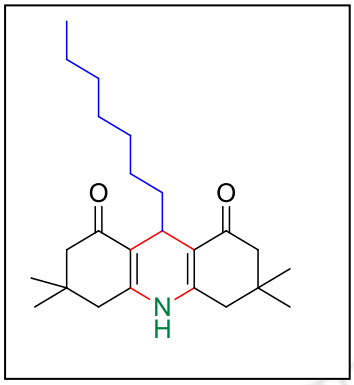
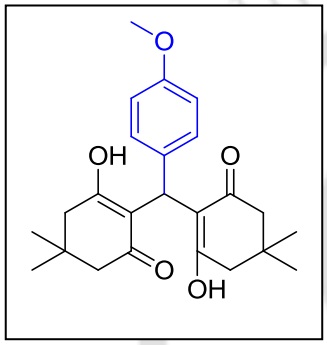
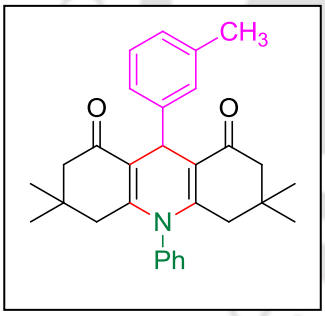


9-Heptyl-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.8h):[29]

Yellow Solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.07 (s, 1H), 4.08 (t, *J* = 5.0 Hz, 1H), 2.35-2.18 (m, 8H), 1.43-1.42 9m, 2H), 1.29-1.09 (m, 22H), 0.83 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.9, 148.9, 113.2, 51.0, 41.4, 35.1, 32.6, 32.0, 30.0, 29.9, 29.5, 27.3, 27.2, 25.5, 22.7, 14.2.



2,2'-((4-Methoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone)(B):[30] White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.90 (s, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 7.5 Hz, 2H), 5.48 (s, 1H), 3.77 (s, 3H), 2.54-2.19 (m, 8H), 1.22 (s, 6H), 1.10 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 190.5, 189.5, 157.8, 130.0, 127.9, 115.9, 113.8, 55.3, 47.2, 46.6, 32.2, 31.5, 29.7, 27.5.



3,3,6,6-Tetramethyl-10-phenyl-9-(m-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3.7cc):[31]

White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57-7.55 (m, 3H), 7.30 (s, 1H), 7.23 (d, *J* = 6.7 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.2 Hz, 1H), 5.25 (s, 1H), 2.31 (s, 3H), 2.16 (ABq, *J* = 16.2 Hz, 4H), 2.07 (d, *J* = 17.4 Hz, 2H), 1.82 (d, *J* = 17.4 Hz, 2H), 0.94 (s, 6H), 0.81 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 195.8, 149.7, 146.2, 139.4, 137.4, 129.4, 129.3, 128.0, 126.9, 124.7, 114.9, 50.4, 41.9, 32.6, 32.5, 29.8, 26.9, 21.7.

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3.5. ^{1}H and ^{13}C NMR spectra of the products:

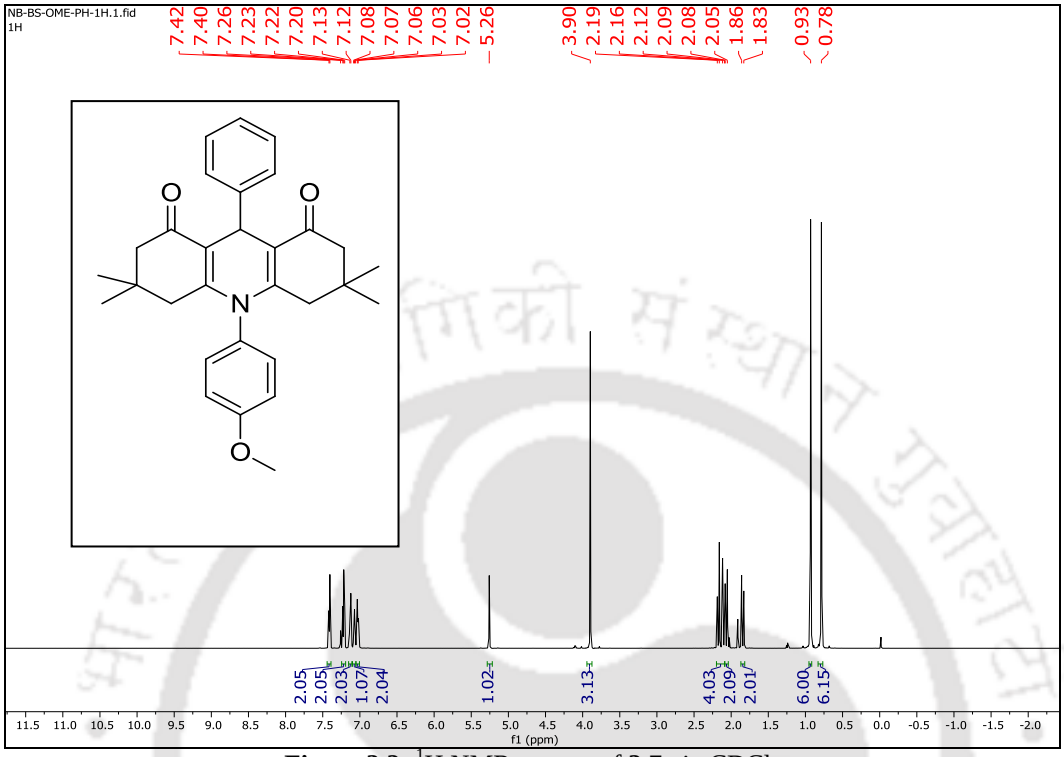

Figure 3.2: ^{1}H NMR spectra of **3.7a** in $CDCl_3$

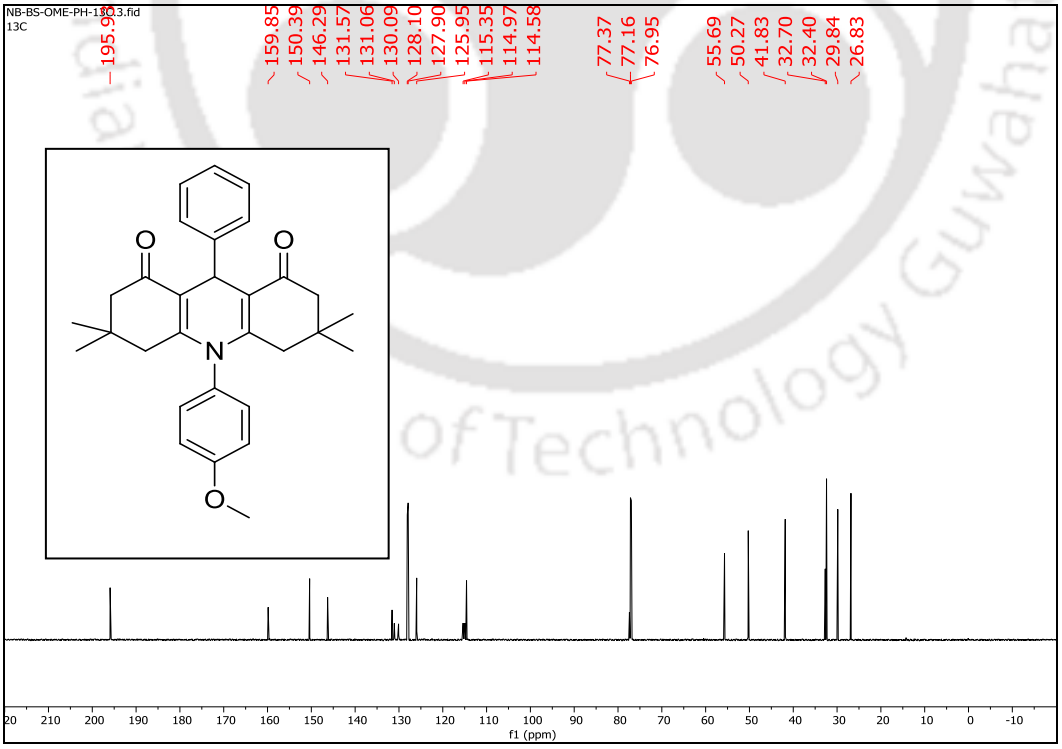

Figure 3.3: ^{13}C NMR spectra of **3.7a** in $CDCl_3$

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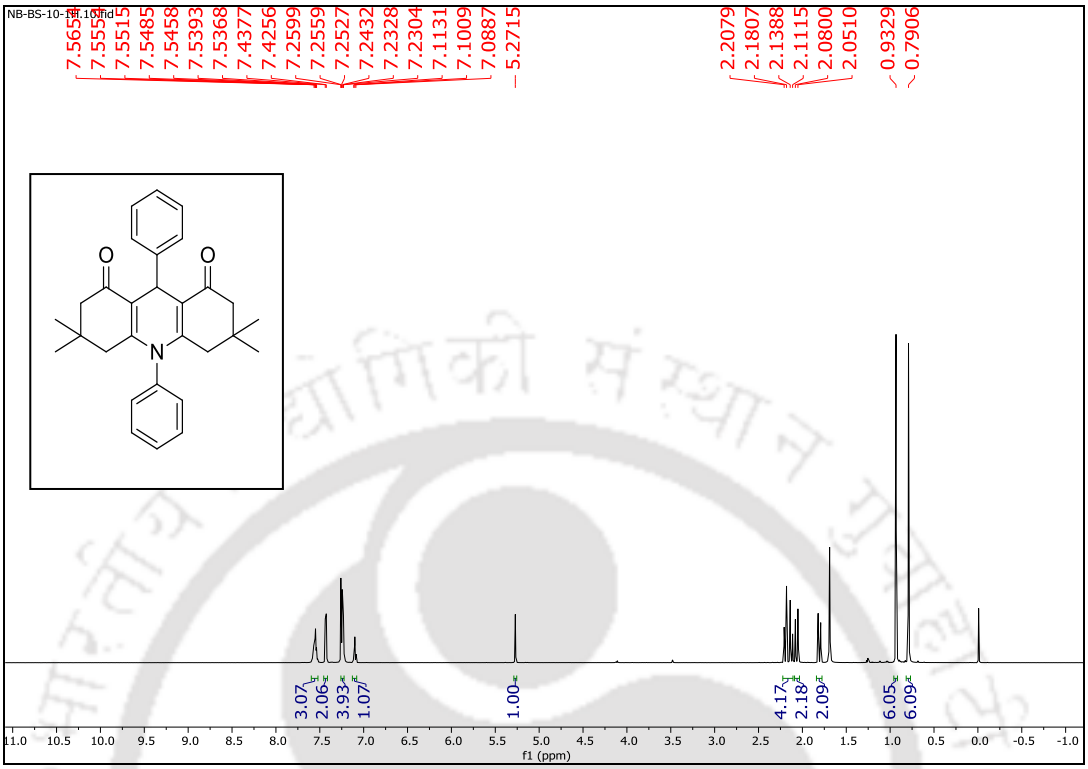

Figure 3.4: ^{1}H NMR spectra of **3.7b** in $CDCl_3$

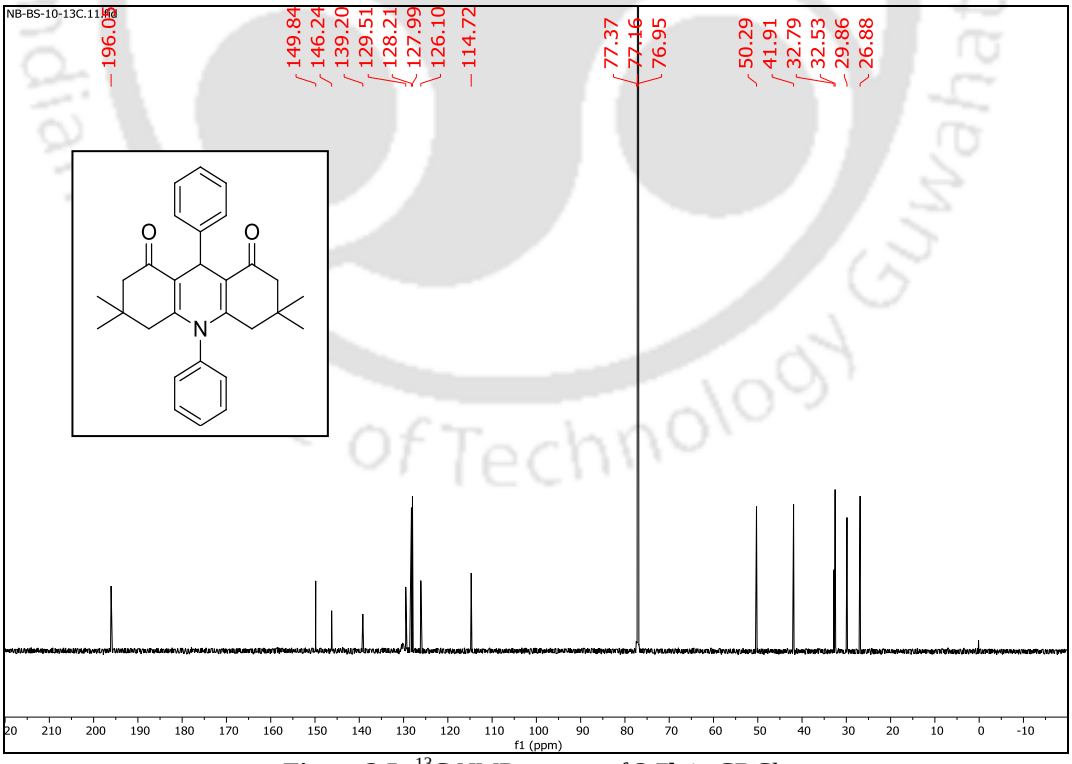

Figure 3.5: ^{13}C NMR spectra of **3.7b** in $CDCl_3$

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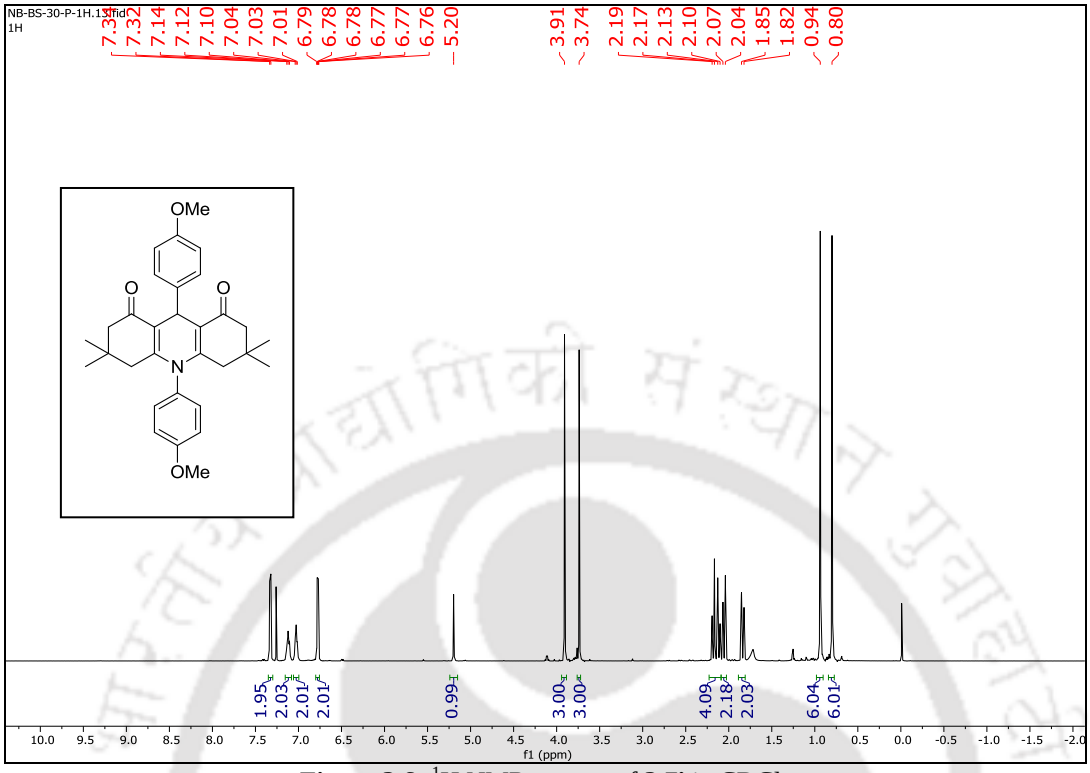

Figure 3.6: ^{1}H NMR spectra of **3.7i** in $CDCl_3$

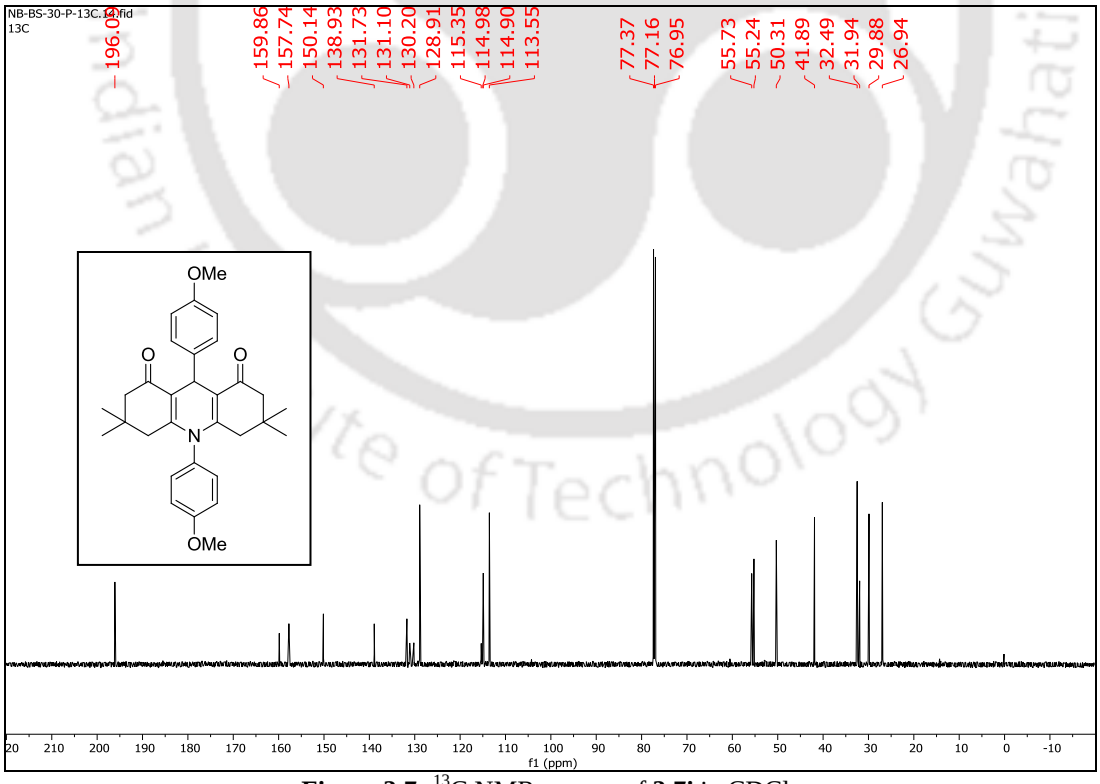

Figure 3.7: ^{13}C NMR spectra of **3.7i** in $CDCl_3$

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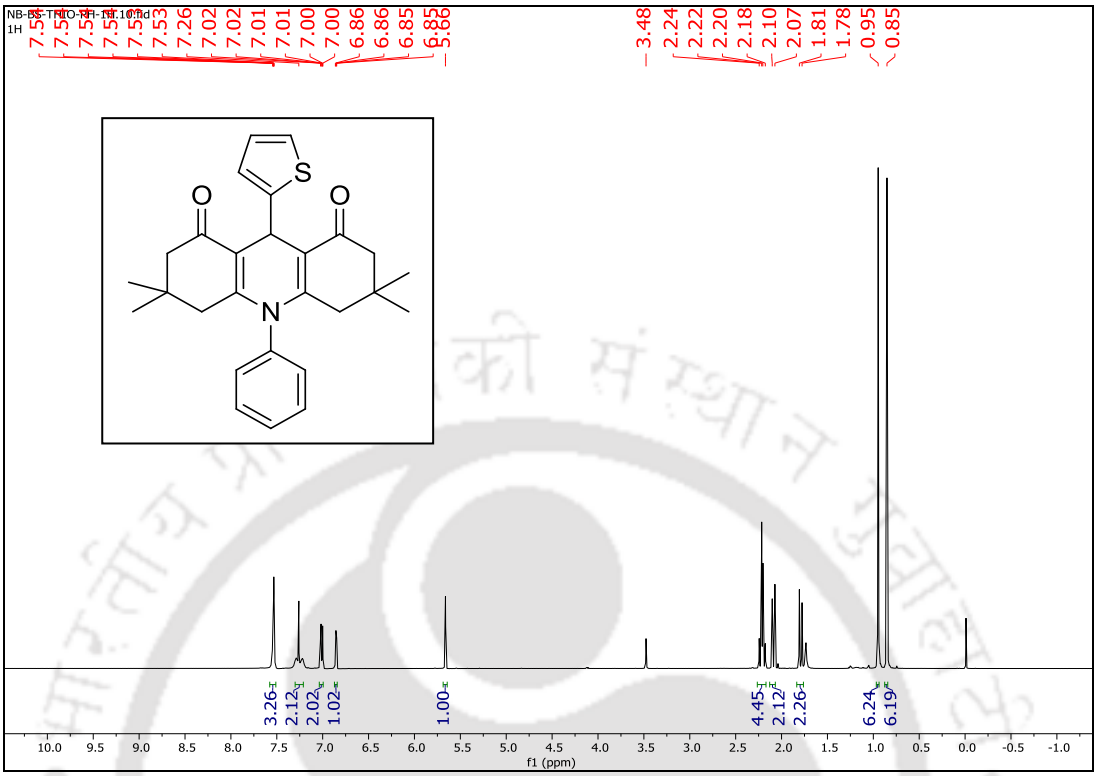

Figure 3.8: ^{1}H NMR spectra of **3.7n** in $CDCl_3$

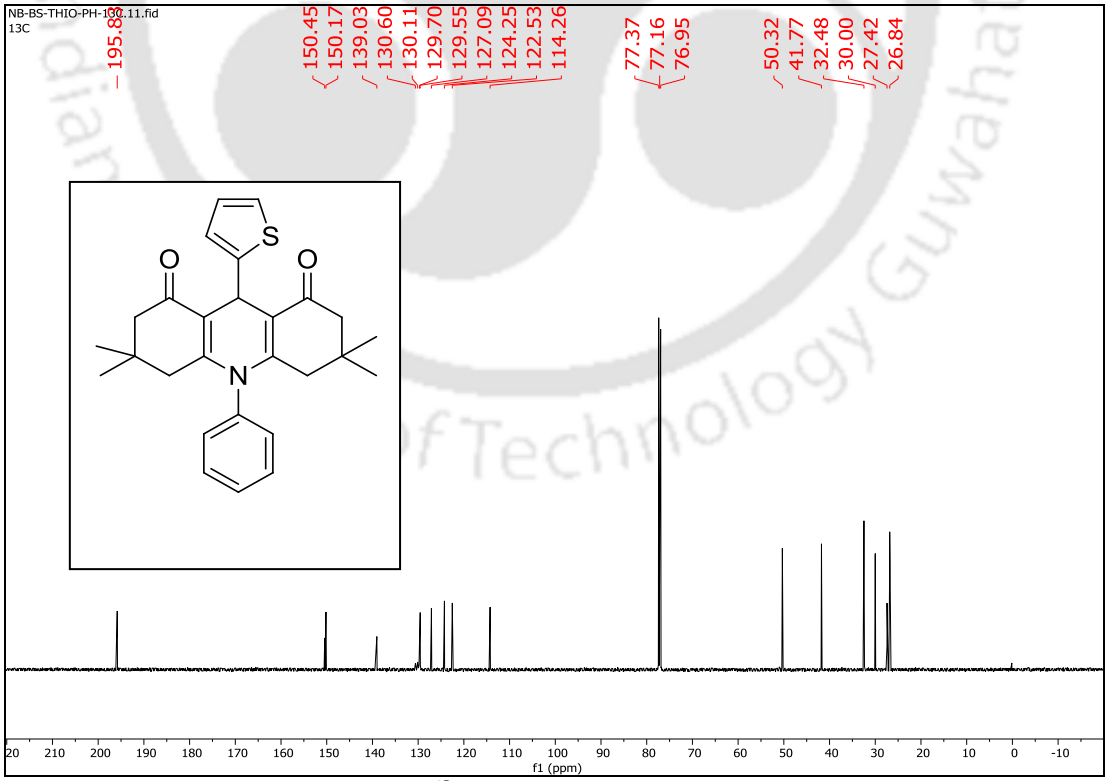

Figure 3.9: ^{13}C NMR spectra of **3.7n** in $CDCl_3$

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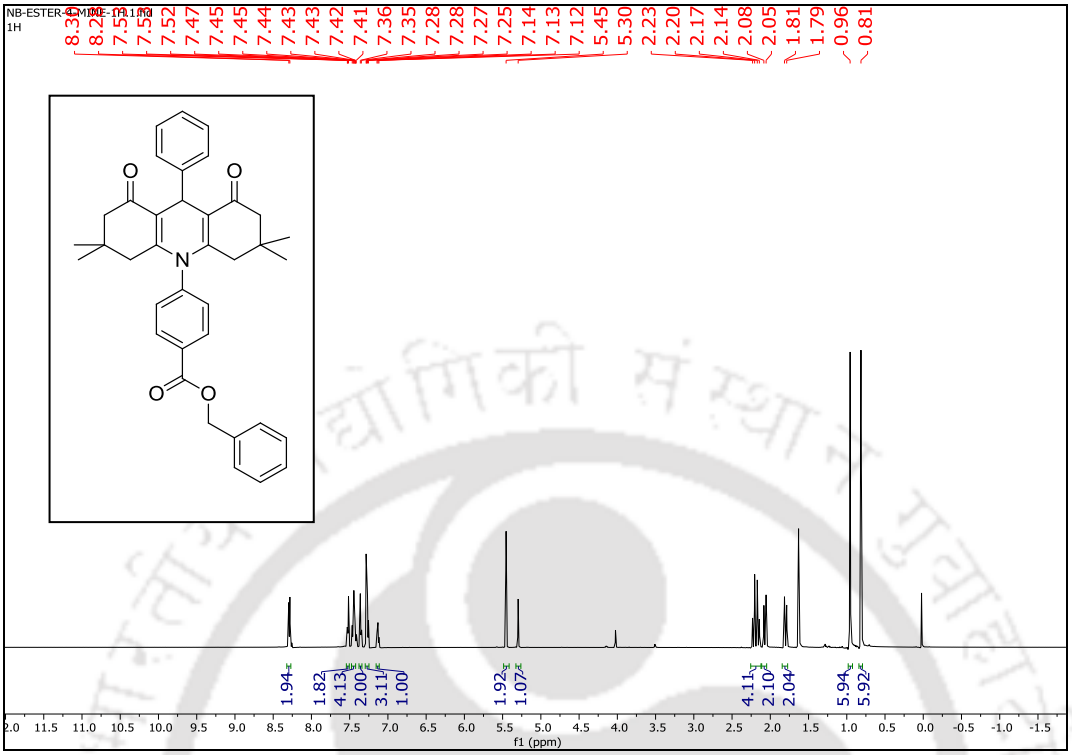

Figure 3.10: ^{1}H NMR spectra of **3.7u** in $CDCl_3$

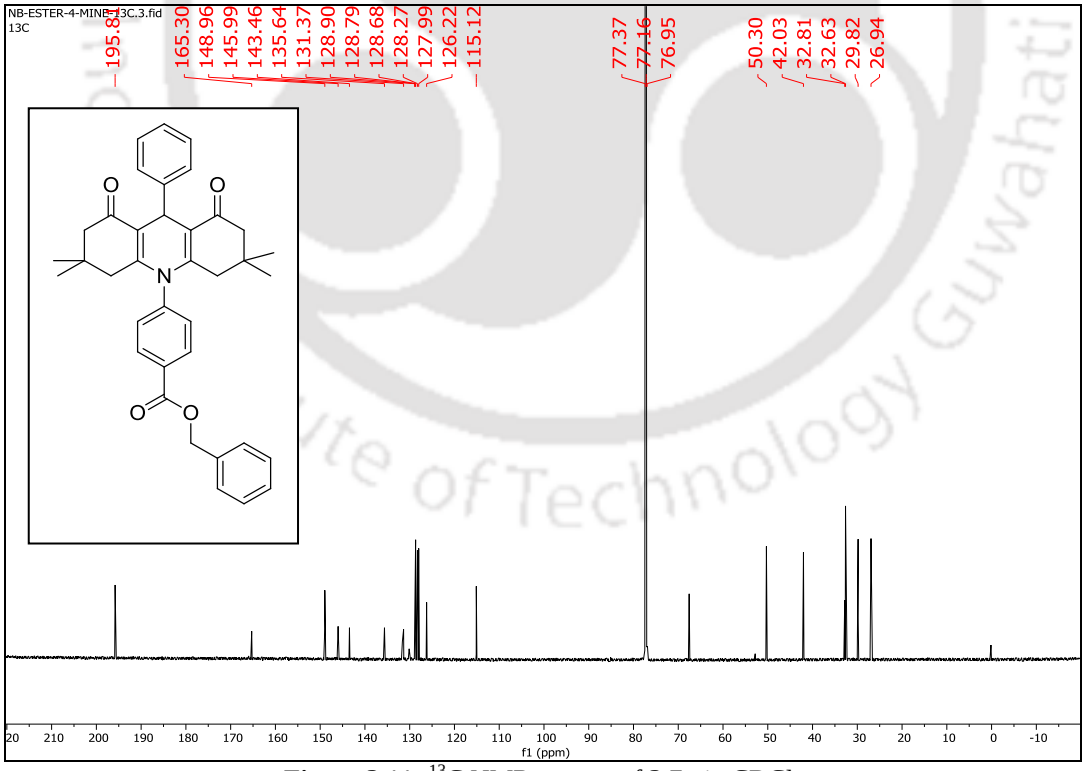

Figure 3.11: ^{13}C NMR spectra of **3.7u** in $CDCl_3$

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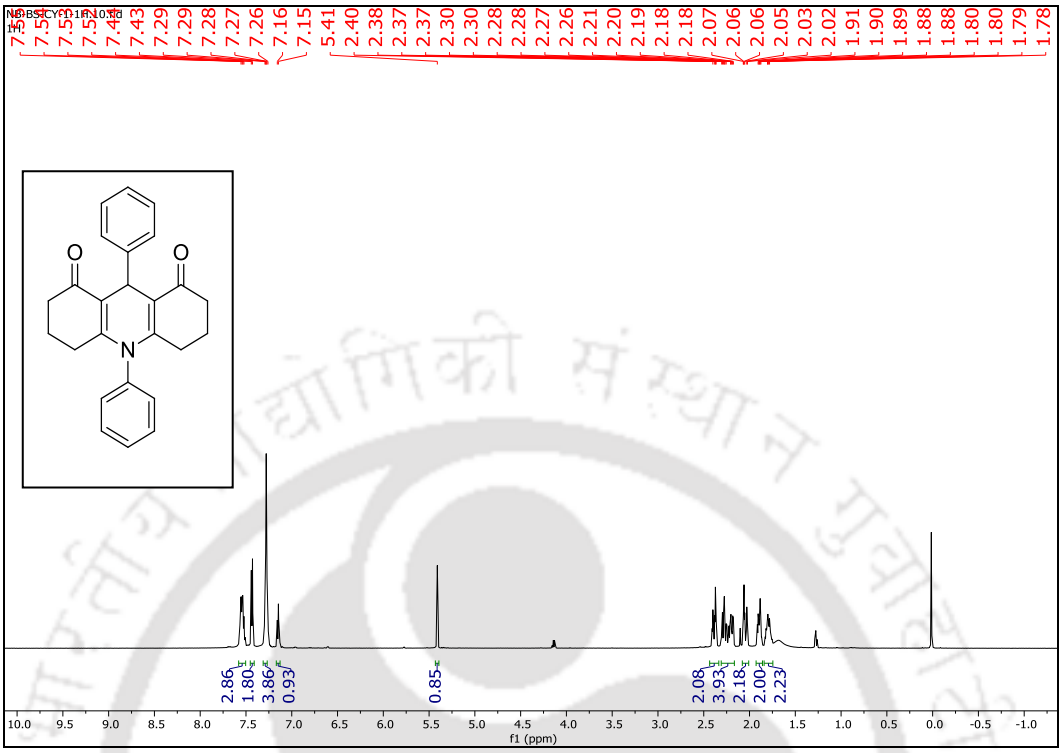

Figure 3.12: ^{1}H spectra of **3.7aa** in $CDCl_3$

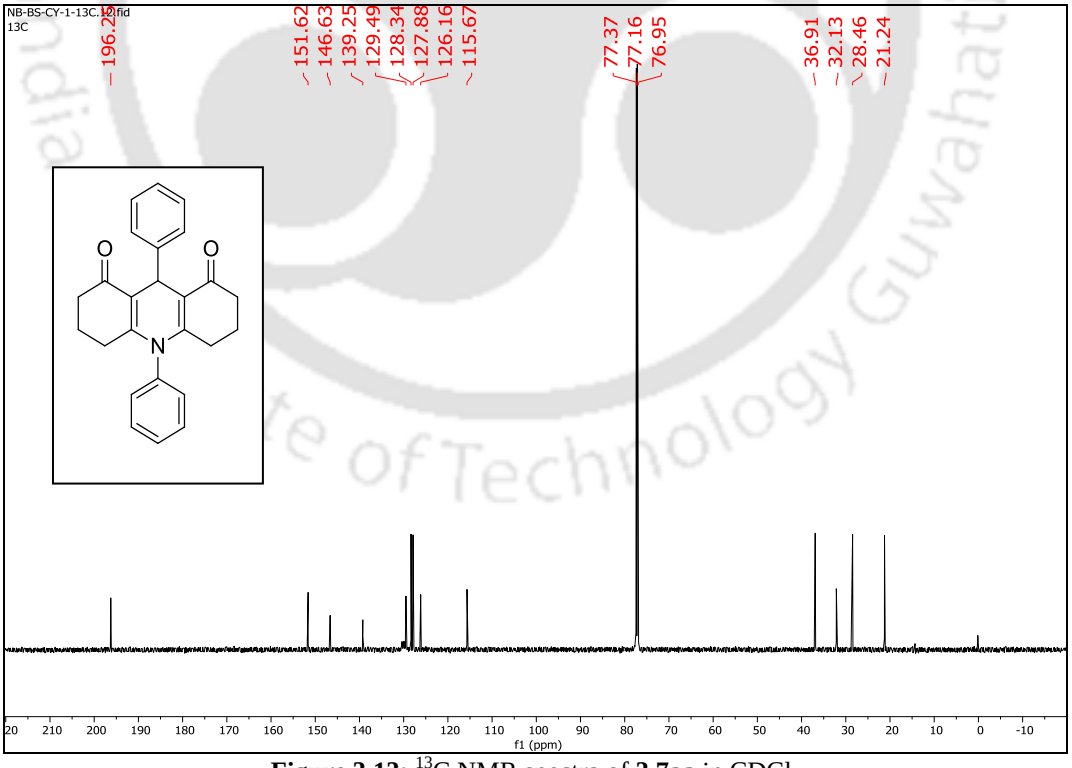

Figure 3.13: ^{13}C NMR spectra of **3.7aa** in $CDCl_3$

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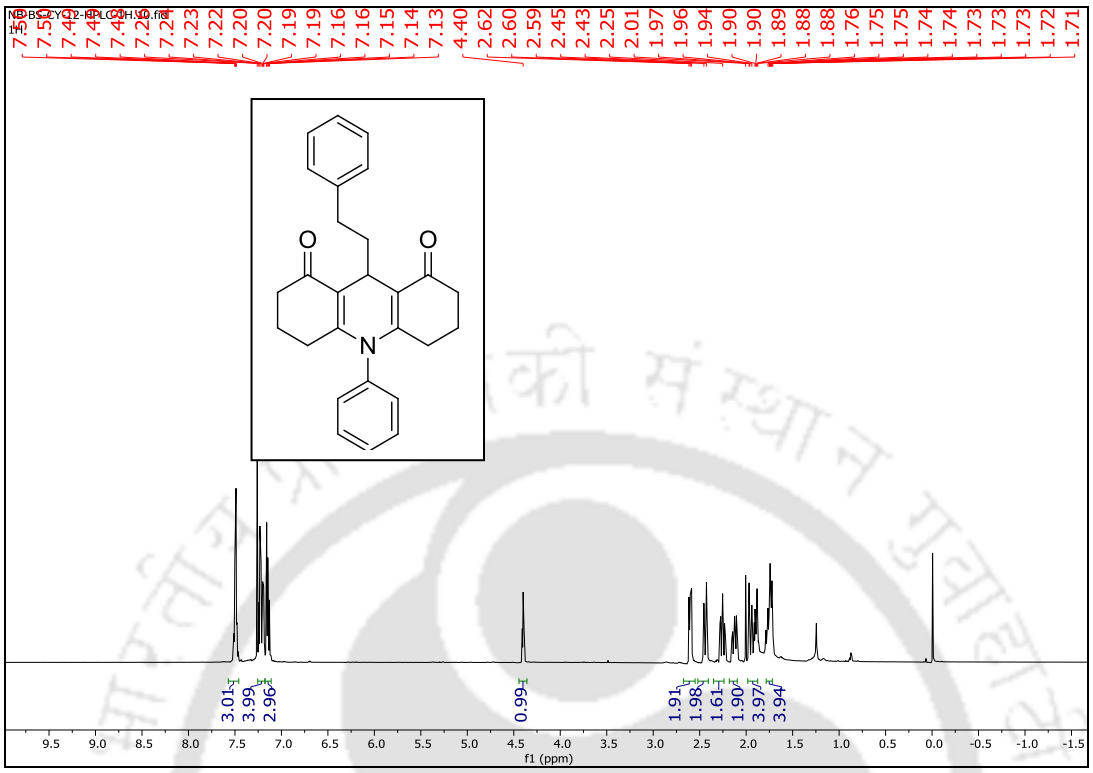

Figure 3.14: ^{1}H NMR spectra of **3.7af** in $CDCl_3$

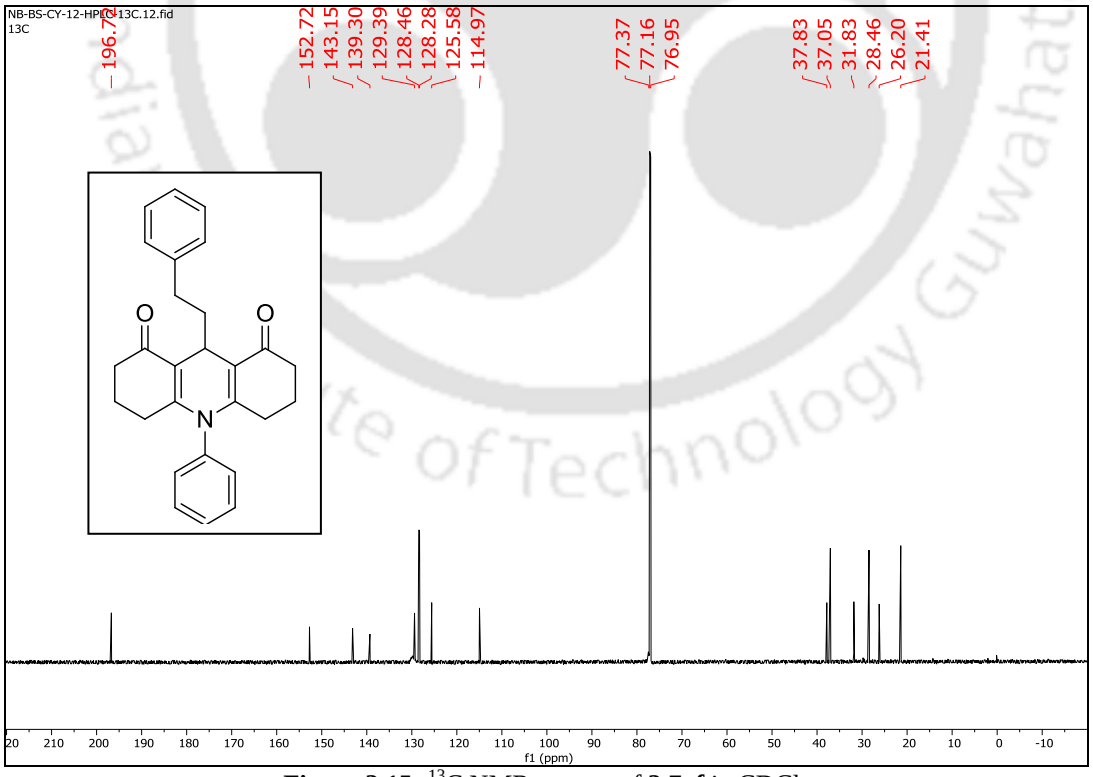

Figure 3.15: ^{13}C NMR spectra of **3.7af** in $CDCl_3$

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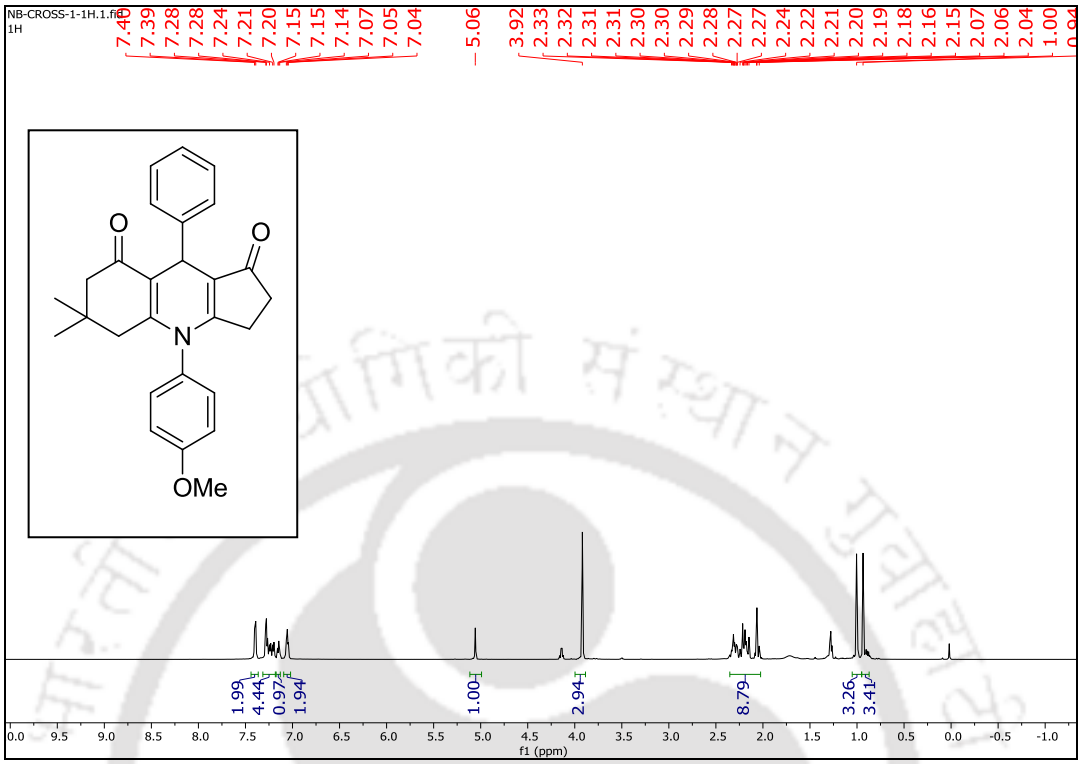

Figure 3.16: ^{1}H NMR spectra of **3.7am** in $CDCl_3$

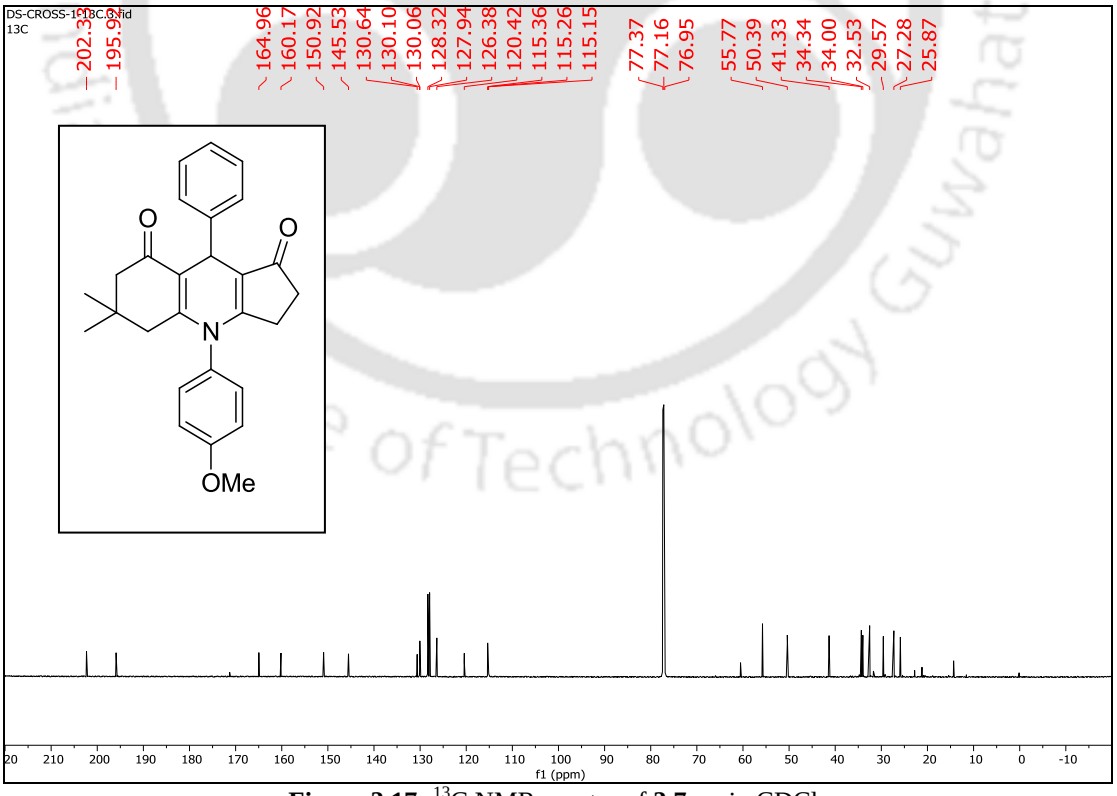

Figure 3.17: ^{13}C NMR spectra of **3.7am** in $CDCl_3$

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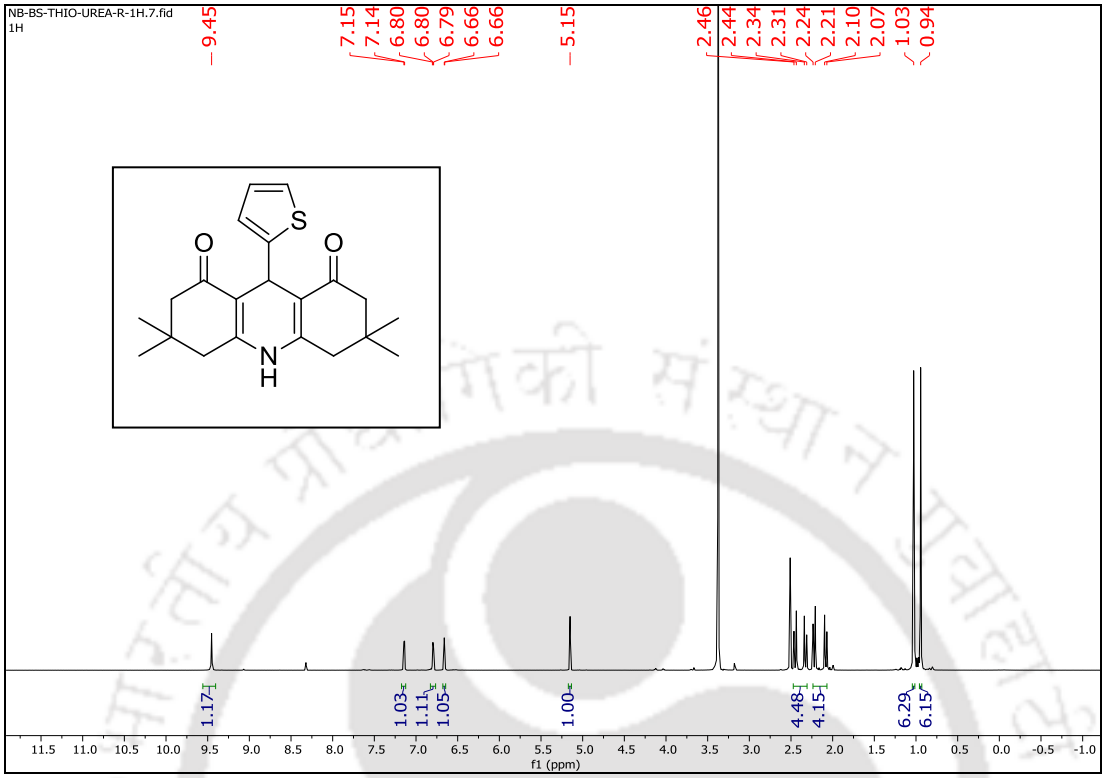

Figure 3.18: ^{1}H NMR spectra of **3.8f** in $CDCl_3$

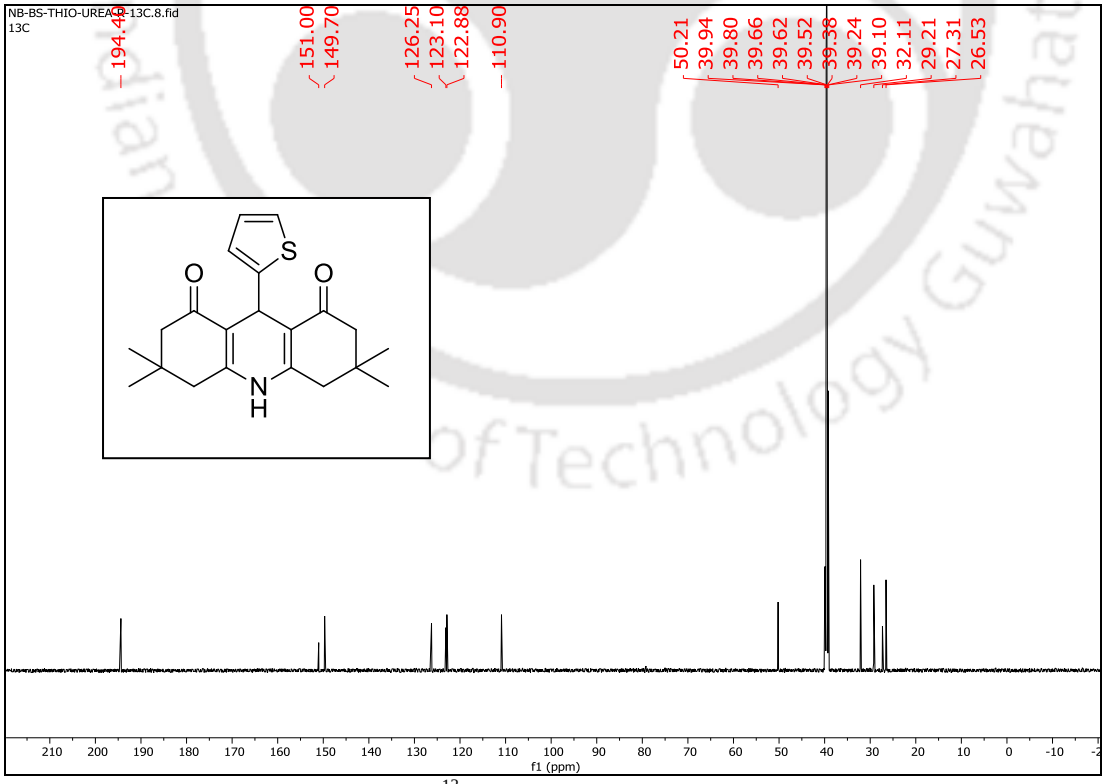

Figure 3.19: ^{13}C NMR spectra of **3.8f** in $CDCl_3$

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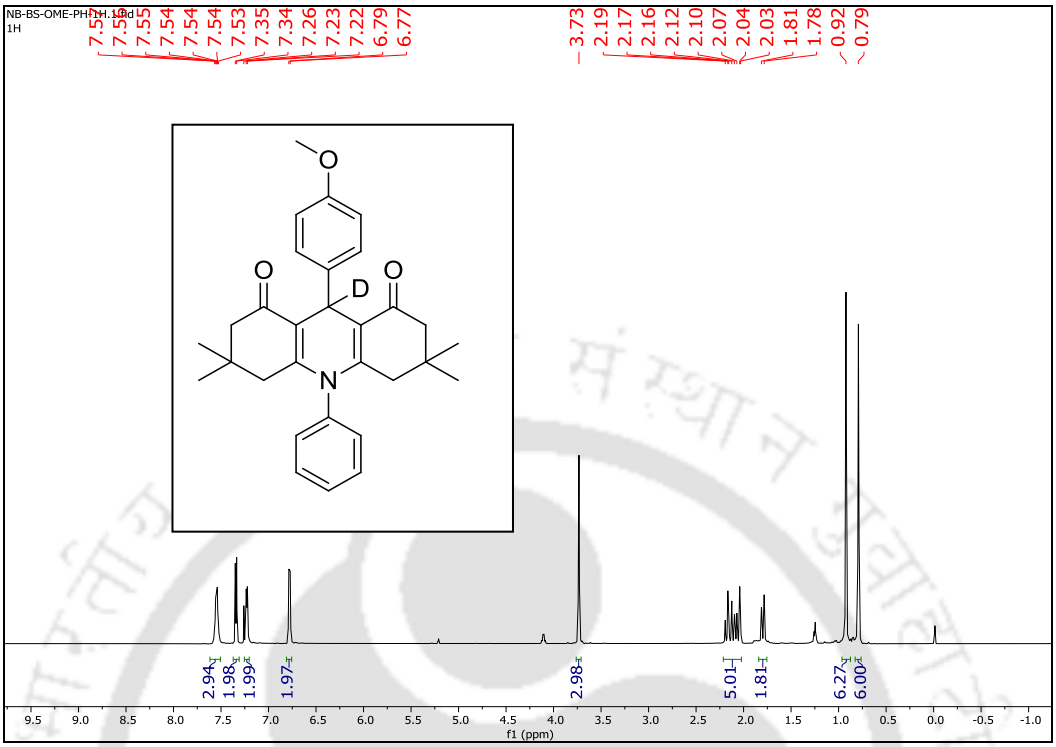

Figure 3.20: ^{1}H NMR spectra of **3.7d'** in $CDCl_3$

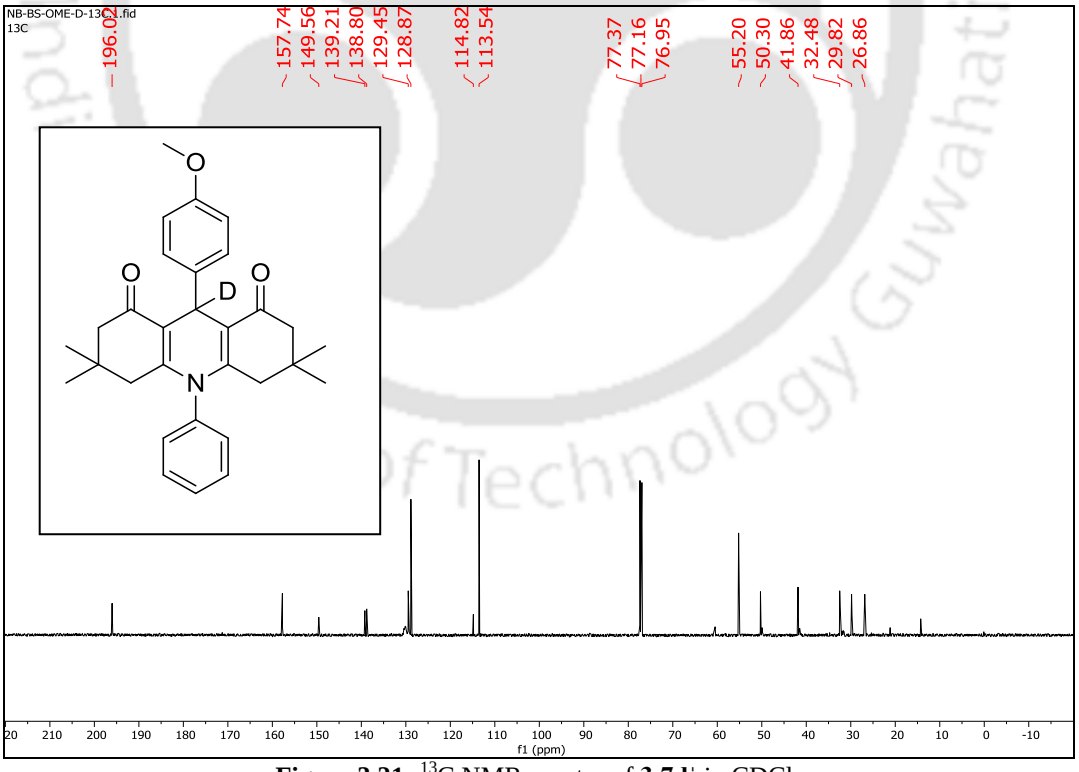

Figure 3.21: ^{13}C NMR spectra of **3.7d'** in $CDCl_3$

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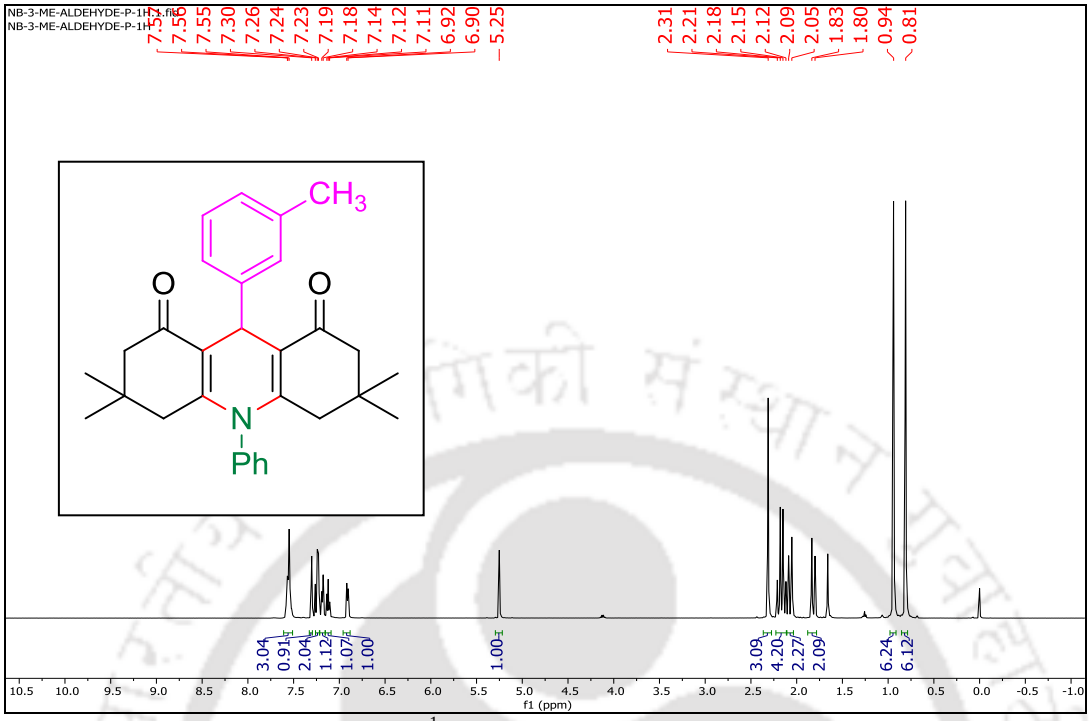

Figure 3.22: ^{1}H NMR spectra of **3.7cc** in $CDCl_3$

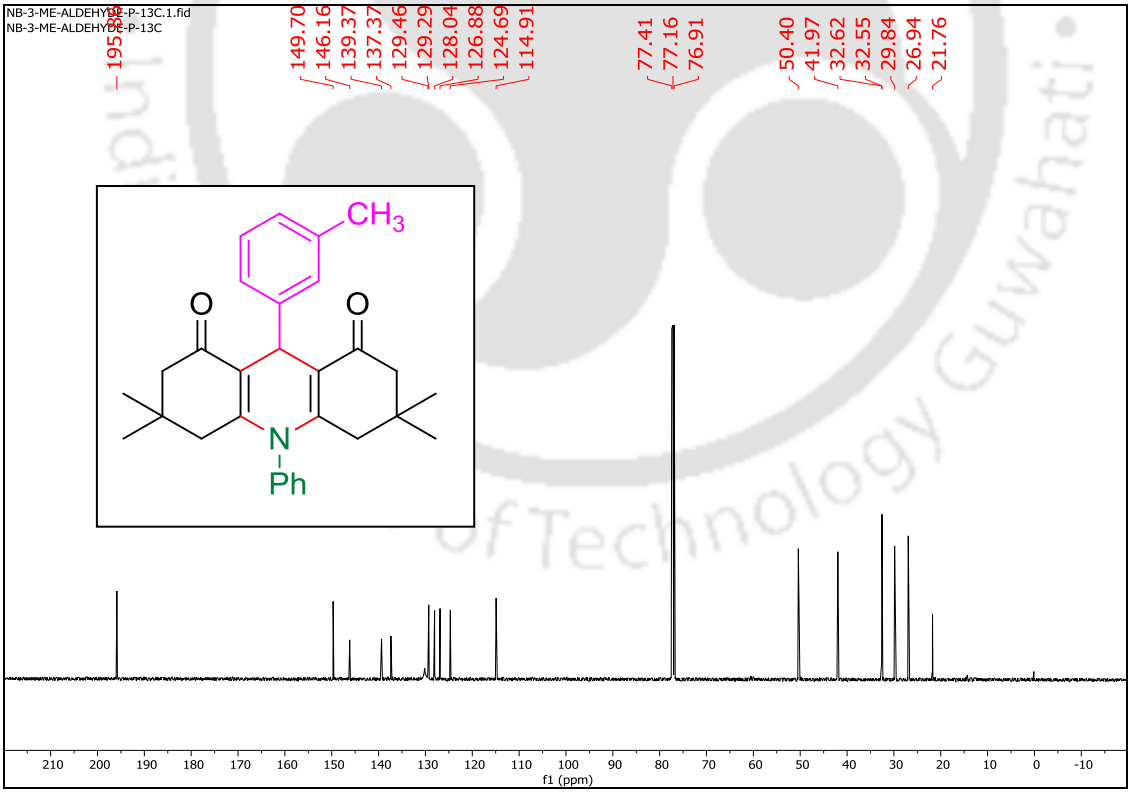

Figure S64: ^{13}C NMR spectra of **3.7cc** in $CDCl_3$

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Chapter 4

Ruthenium Pincer Complex Catalyzed Selective Synthesis of C-3 Alkylated Indoles and Bis(indolyl)methanes Directly from Indoles and Alcohols

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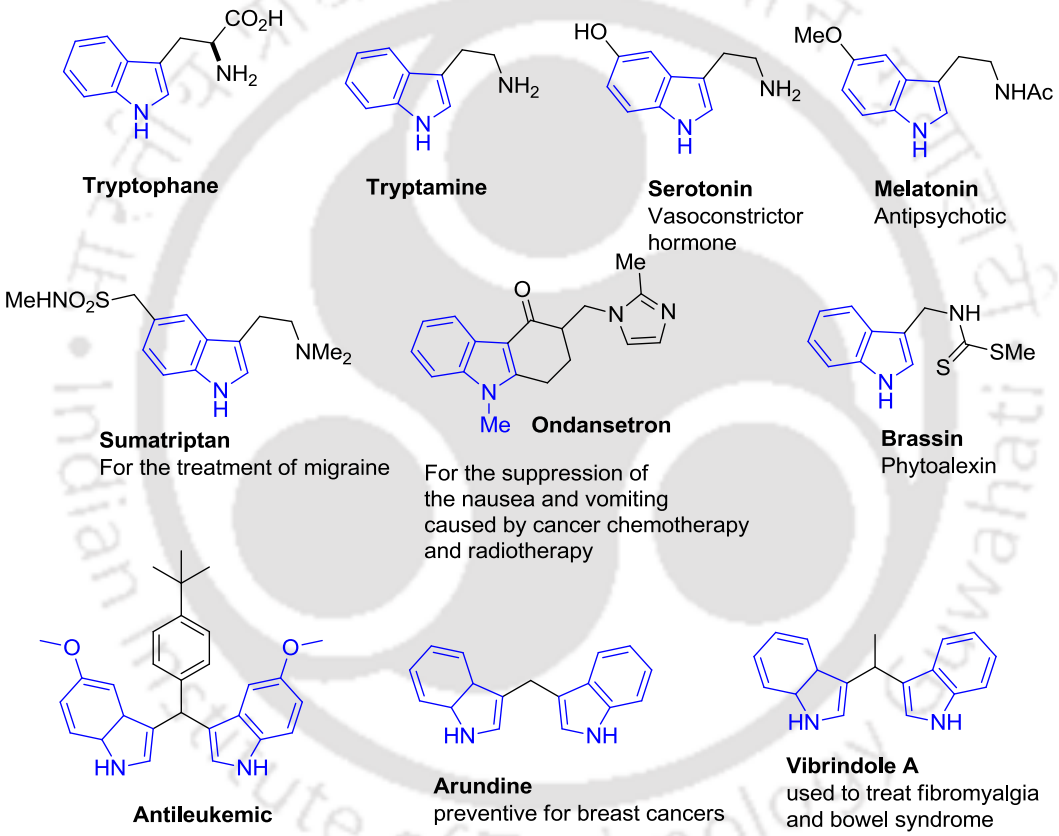
4.1. Introduction:

Indoles and their derivatives are considered as one of the most important heterocyclic scaffolds because of their prevalence in many bioactive compounds,[1] (Scheme **4.1**) natural products,[2] pharmaceuticals,[3] agro-chemicals[4] and functional materials.[5] Thus, the synthesis and functionalization of indole moiety have attracted significant attention.



Scheme 4.1: Biologically important indole moiety

However, classical approach[6] for the synthesis of indole moiety or its selective functionalization[7] involves the use of toxic reagents, harsh reaction condition and/or pre-functionalization of substrates, which generates substantial amount of waste materials. Hence the development of green, atom-efficient and sustainable strategies for the synthesis of indole as well as C-3 functionalization of this scaffold is an area of intense

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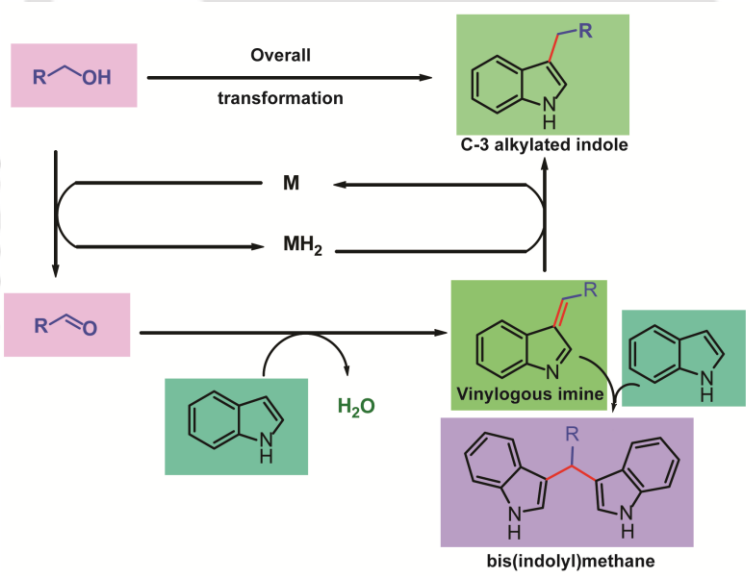
research. In this perspective, acceptorless dehydrogenative (AD) synthesis of indole is considered as highly atom-economical and environmentally benign approach. Likewise C-3 alkylation[8] of 1H-indole using alcohols as alkylating agents *via* borrowing hydrogen catalysis (BH)[9] is extremely advantageous over conventional Friedel-Crafts type reaction,[7a] as it does not require any Lewis and Brønsted acids[7b] or organocatalysts.[7d] The only byproduct formed in the process is water, which makes the overall system environmentally benign. The strategy comprises of three steps i) dehydrogenation of alcohol to form carbonyl compound ii) condensation reaction to form a α,β–unsaturated imine (vinylogous imine) derivative iii) hydrogenation of α,β–unsaturated imine derivative to C-3 alkylated indole (Scheme **4.2**). In the third step, before hydrogenation, another molecule of indole may attack to the vinylogous imine derivative to form biological important bis(indolyl)methane scaffold.[10] Thus selective synthesis of C-3 alkylated indole and bis(indolyl)methane is important.



Scheme 4.2. Alkylation of 1H-indole *via* the borrowing hydrogen strategy

In 2007, *Grigg and coworkers*[11] first demonstrated $[Cp^*IrCl_2]_2$ catalyzed C-3 alkylation of indoles *via* indirect functionalization of primary alcohols (Scheme **4.3**).

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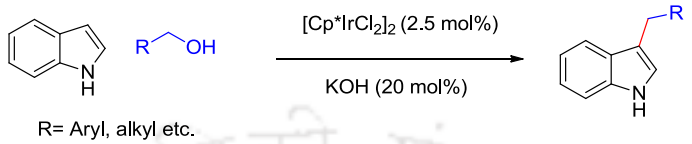
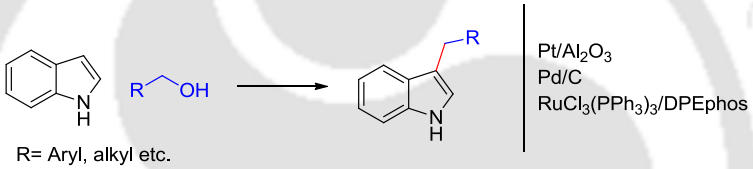
Next, *Shimizu and coworkers*[12] reported heterogeneous Pt-catalyzed C-3 alkylation of indoles with a diverse range of aliphatic alcohols (Scheme **4.4**). However, their protocol failed to achieve alkylation of indoles with the secondary alcohols.



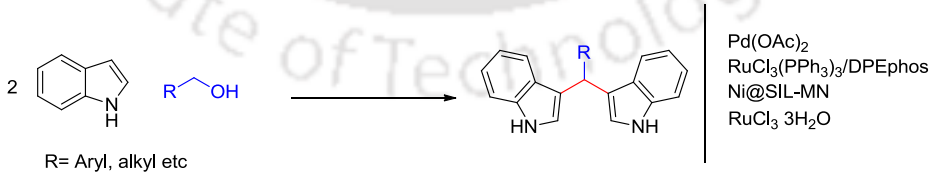
Scheme 4.3: Iridium catalyzed C-3 alkylation of indoles with alcohols

The C-3 alkylation of indoles with alcohols as alkylation agent was also well explored with Pd[8d] and Ru[8d] catalyst.



Scheme 4.4: C-3 alkylation of indole using alcohol *via* homogeneous and heterogeneous catalyst

The synthesis of bis(indolyl)methane derivatives from indoles and alcohols gets significant attention in organic synthesis, as they are found in many natural products and bioactive compounds.[13] So, the selective synthesis of bis(indolyl)methane derivatives directly from indole with activated benzyl alcohols has also been explored[14,8d] (Scheme **4.5**).



Scheme 4.5: Synthesis of bis(indolyl)methane with homogeneous and heterogeneous catalyst

The synthesis of indole and its functionalization in one pot to achieve C-3 functionalized is highly challenging as it involves multiple reaction steps. Recently, synthesis of C-3 alkylated indoles was achieved directly from indolines and aliphatic

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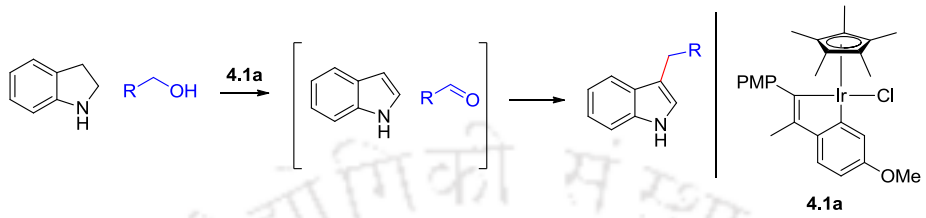
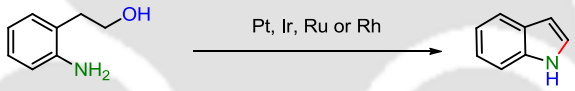
primary alcohols in the presence of iridium catalyst[15] (Scheme **4.6**). In this approach indole was first formed by the dehydrogenation of indoline and then it undergoes C-3 alkylation to achieve the targeted scaffold.

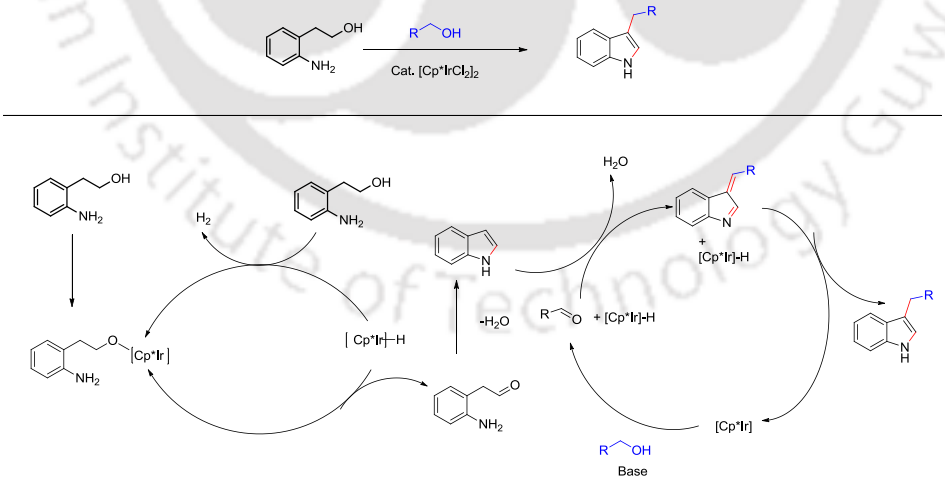


Scheme 4.6: Synthesis of C-3 alkylated indole directly from indoline with iridium catalyst

The transition metal catalyzed dehydrogenative synthesis of indoles[16] directly from 2-aminophenethyl alcohol has been reported (Scheme **4.7**). The group of Yamaguchi disclosed one pot synthesis of indole and its functionalization to afford C-3 alkylated indole directly from 2-(2-aminophenyl)ethan-1-ol and primary alcohol.



Scheme 4.7: Synthesis of indole from 2-(2-aminophenyl)ethan-1-ol



Scheme 4.8: Proposed mechanism for the one-pot, tandem oxidative cyclization/alkylation of 2-aminophenyl ethyl alcohol and primary alcohols to afford substituted indoles

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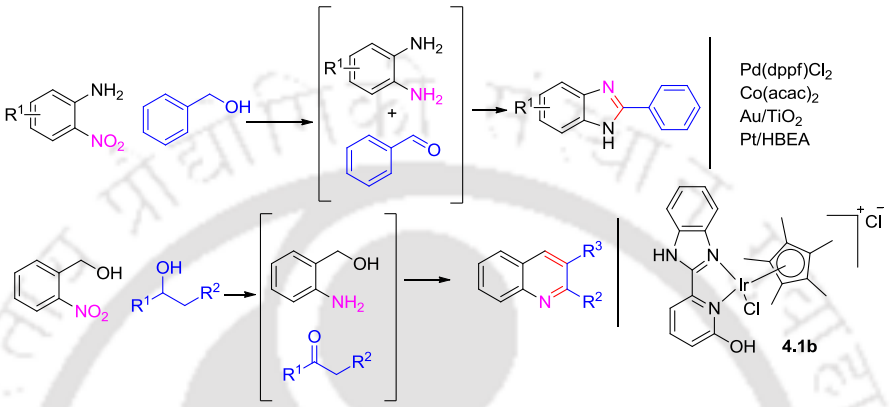
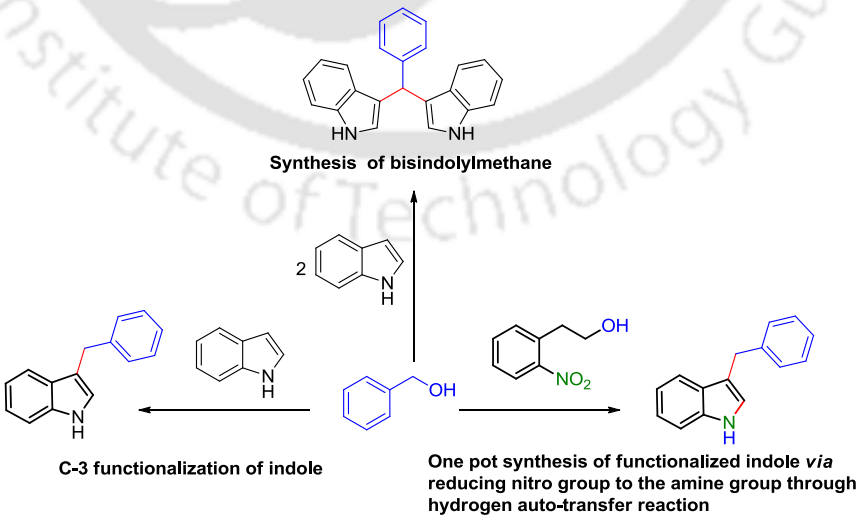
Recently, the strategy of reducing the nitro group to the amine group *via* hydrogen auto-transfer and subsequent condensation with the formed carbonyl compounds showed their efficacy toward the synthesis of heterocyclic compounds[17,16d,11] (Scheme **4.9**).



Scheme 4.9: Synthesis of different heterocycle from different nitro-derivatives

Thus, the development of a catalyst which can selectively form C-3 functionalized indoles and bis(indolyl)methane derivatives using diverse range of primary and secondary alcohols as alkylating agents is highly desirable. Moreover, the synthesis and functionalization of indole in one pot *via* reducing nitro group to the amine group *via* hydrogen auto-transfer reactions would also be interesting (Scheme **4.10**).



Scheme 4.10: Synthesis and functionalization of indole in one pot

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4.2. Present Work:

Chapter 4 demonstrated SNS-acridine ligand derived Ru-pincer complex catalyzed C-3 alkylation of indoles to get 3-substituted indoles. Moreover, the selective synthesis of bis(indolyl)methane derivatives was also described. Furthermore, the one pot synthesis of C-3 alkylated indoles was also achieved directly from 2-(2-nitrophenyl)ethan-1-ol and primary alcohols *via* sequential multistep reaction.

4.2.1. Optimization of reaction conditions:

At the outset, the catalytic applicability of complex **2.1A-2.3A** toward the C-3 alkylation of indoles with various primary alcohols was examined. To find out the optimum reaction conditions, various reaction parameters were screened employing indole and 1-octanol as model substrates. When, a mixture of indole (1 mmol), 1-octanol (1 mmol) and KOH (1 mmol) was heated at 135 $^{\circ}$C under neat condition for 18 h in Ace pressure tube in the presence of 1 mol % catalyst **2.1A**, 10% 3-octyl-1H-indole (**4.6e**) was obtained along with 65% 3,3'-(octane-1,1-diyl)bis(1H-indole) (**4.7d**) (Table **4.1**, entry **1**). Thus, to improve the yield of the 3-octyl-1H-indole (**4.6e**), the ratio of indole: 1-octanol was increased. Hence, when the reaction was performed under the similar conditions taking indole: 1-octanol ratio 1:5, 40% **4.6e** was isolated (Table **4.1**, entry **4**). Gratifyingly, the yield of **4.6e** was improved from 40% to 86% just by lowering the amount of KOH to 0.5 mmol (Table **4.1**, entry **5**). Further decrease in the amount of the base was found to have detrimental effect to the yield of the desired 3-octyl-1H-indole (Table **4.1**, entry **7**). With catalytic amount of base (5 mol %) the product formation was not happened (Table **4.1**, entry **8**). After 10 h, the yield of the desired product was 60% (Table **4.1**, Entry **10**). Bases like Cs_2CO_3, ^{t}BuOK and NaOH gave moderate yield (Table **4.1**, entries **11-13**) under the similar reaction conditions, whereas $CsOH.H_2O$ and Na_2CO_3 gave poor yield (Table **4.1**, entries **14** and **15**). Thus, the observed selectivity is highly dependent on the nature and stoichiometry of the applied base and amount of alkylating agent.

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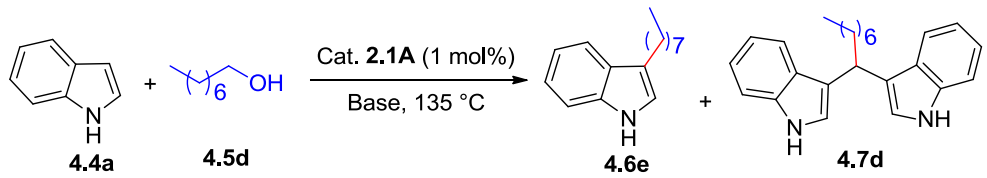
Table 4.1. Optimization of the reaction condition for the C-3 alkylation of indole.[a]



4.4a **4.5d** **4.6e** **4.7d**

Entry	Cat.	Base (mmol)	Indole:alcohol	Time (h)	Yield (%)	
					4.6e	**4.7d**
1	**2.1A**	KOH (1)	1:1	18	10	65
2	**2.1A**	KOH (1)	1:3	18	20	60
3	**2.1A**	KOH (1)	1:4	18	30	45
4	**2.1A**	KOH (1)	1:5	18	40	43
5	**2.1A**	KOH (0.5)	1:5	18	86	-
6	**2.1A**	KOH (0.5)	1:3	18	60	10
7	**2.1A**	KOH (0.25)	1:5	18	48	25
8	**2.1A**	KOH (0.05)	1:5	18	-	-
9[b]	**2.1A**	KOH (0.5)	1:1	18	10	60
10	**2.1A**	KOH (0.5)	1:5	10	60	-
11	**2.1A**	Cs_2CO_3 (0.5)	1:5	18	65	-
12	**2.1A**	^tBuOK (0.5)	1:5	18	70	-
13	**2.1A**	NaOH (0.5)	1:5	18	70	-
14	**2.1A**	$CsOH.H_2O$ (0.5)	1:5	18	30	-
15	**2.1A**	Na_2CO_3 (0.5)	1:5	18	5	-
16	**2.2A**	KOH (0.5)	1:5	18	30	-
17	**2.3A**	KOH (0.5)	1:5	18	25	-
18[c]	**2.1A**	KOH (0.5)	1:5	24	60	-
19	-	KOH (0.5)	1:5	24	-	-
20	**2.1A**	-	1:5	24	-	-

[a]Reaction conditions: indole (1 mmol), 1-octanol (5 mmol), cat **2.1A** (0.01 mmol, 1 mol%), 30 mL Ace pressure tube, 135 °C, 18 h. [b]In toluene (1 mL). [c]0.5 mol % catalyst **2.1A** loading.

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The reaction was also carried out with solvent such as toluene (Table **4.1**, entry **9**) where the yield of the desired C-3 alkylated indole was found to be very poor. Under the optimized reaction conditions, complex **2.2A** or **2.3A** gave inferior yield of the desired product **4.6e** (Table **4.1**, entries **16** and **17**). With lowering the catalyst loading, the yield of the desired product was diminished (Table **4.1**, entry **18**). Without the presence of any base, catalyst **2.1A** failed to activate the alcohol; similarly, in absence of catalyst **2.1A**, 0.5 mmol KOH did not give any desired 3-octyl-1H-indole (Table **4.1**, entries **19**, **20**). Thus, the above results clearly show the importance of both catalyst and the base for the smooth progress of the reaction.

4.2.2. Substrate scope of C-3 alkylation of indole:

After achieving the optimized reaction condition, the generality and the limitations of the present protocol was explored. To manifest the practical applicability of the system, various alcohols and representative substituted indoles were investigated (Scheme **4.11**). The reactions of indoles with variety of primary aliphatic alcohols afforded C-3 alkylated product in good to excellent yield **4.6a-4.6f** (60-95%). Thermodynamic data suggested that activating methanol to its corresponding formaldehyde required large enthalpy (approx. 31.0 Kcal)[18a] which in many cases can limit the scope of the reaction. In contrast, to our delight, reaction of indole with methanol resulted in excellent conversion to the desired product **4.6a** with yield of 95%. Similarly, ethanol and butanol were also well assessed to result good yield of the desired products **4.6b** and **4.6c** (78% and 60% respectively). Further increasing the chain length of the alcohol does not prove fatal on the yield of the reaction (Scheme **4.11**, entries **4.6d-4.6f**). Intriguing by this result, the attention was moved to probe the reactivity of secondary aliphatic alcohols like 2-butanol, 2-octanol, 2-decanol toward the alkylation of indole. Pleasingly, the reaction afforded excellent yield of the desired products (Scheme **4.11**, entries **4.6g-4.6i**); however, it requires higher loading of catalyst **2.1A** (2 mol%) as well as longer reaction time (36 h). This is a significant improvement compared to the work of Shimizu and coworkers who achieved a low yield of 4% using 2-octanol.[12] Interestingly, cyclic

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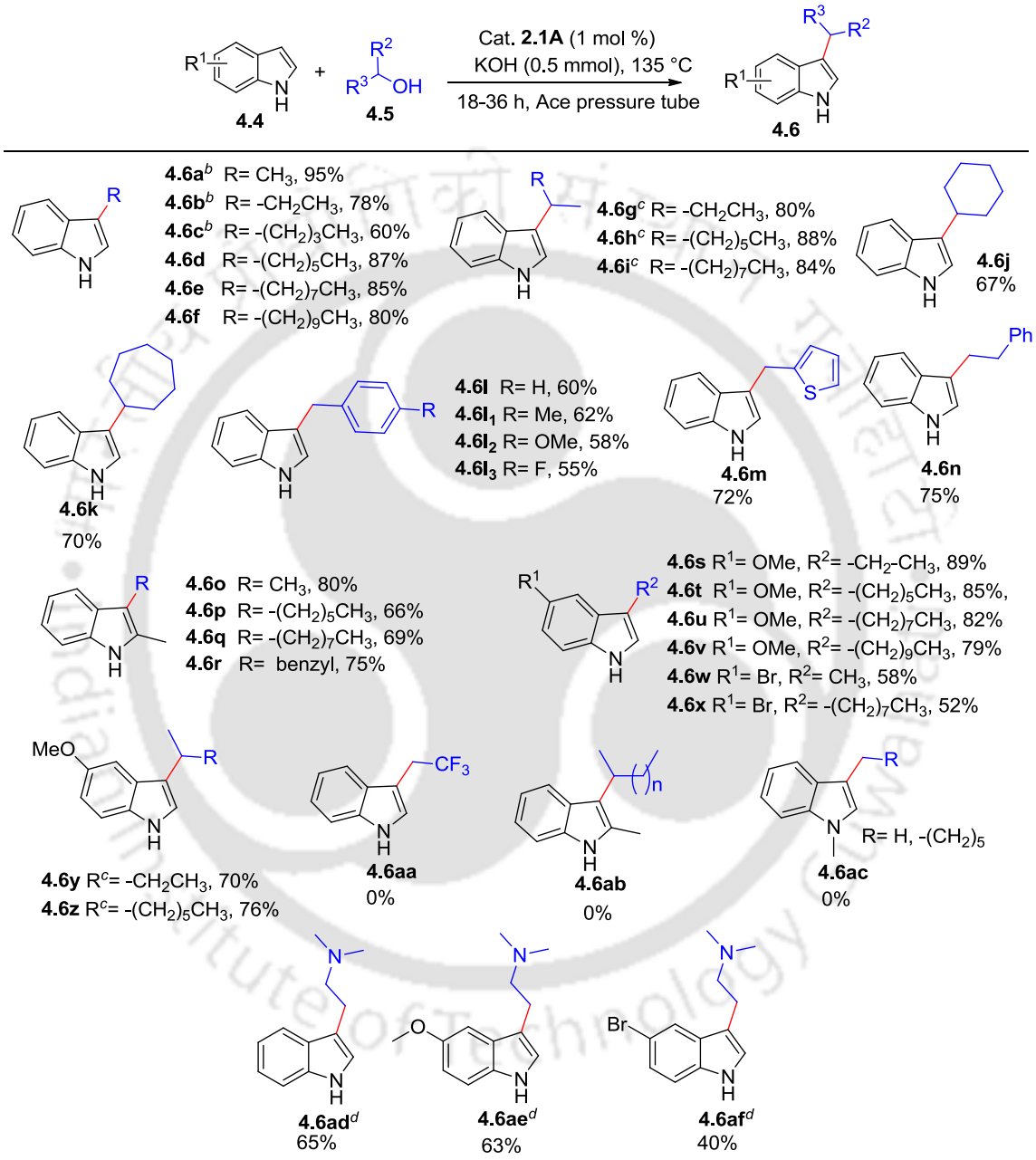
alcohols too could be assessed easily by the present protocol (Scheme **4.11**, entries **4.6j** & **4.6k**). When it came to aromatic alcohols yield



Scheme 4.11. Substrate scope for C-3 alkylation of indole with alcohols.[a] [a]Reaction conditions: indole (1 mmol), alcohol (5 mmol), cat **2.1A** (0.01 mmol, 1 mol%), KOH (0.5 mmol), 30 mL Ace pressure tube, 135 °C, 18-36 h. [b]1 mL alcohol. [c]2 mol % catalyst **2.1A**, 36 h. [d]Catalyst **2.1A** (2 mol %), Cs_2CO_3 (1.1 mmol), 24 h.

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was moderate to good **4.6l-4.6l$_3$** 55%-62%, with useful bis(3-indolyl)phenylmethane[18b-c] derivatives as minor products. Heteroaromatic alcohol like 2-thiophenemethanol works well in this present catalytic system and 72% **4.6m** was isolated. Next, investigation of the reaction of substituted indoles with primary as well as secondary aliphatic alcohols was carried out. 2-Methyl-indole reacted smoothly with primary alcohols to give the corresponding products in high yield **4.6o-4.6r** (66-80%). However in case of secondary aliphatic alcohols, no product formation was observed which might be due to the steric effect cause by methyl group toward incoming alkylating agents.[16e] Indoles with both activating and deactivating groups were compatible with both primary and secondary aliphatic alcohols for C-3 alkylation which afforded good to excellent isolated yield of **4.6s-4.6z** (52-89%). 5-Bromoindole gave moderate yield of the corresponding product **4.6w-4.6x** with some dehalogenated by-product. 2,2,2-Trifluoroethanol failed to activate by this catalyst and no desired **4.6aa** was formed. Also *N*-methylindole did not undergo C-3 alkylation (Scheme **4.11**, entry **4.6ac**), which indicate that anion generated on nitrogen atom in the presence of base plays an important role in this reaction. To examine the practical applicability of the present protocol, the study has been extended to synthesize tryptamine based alkaloid derivatives, which are known for their biological importance.[19] Conventionally, 2-(5-methoxy-1H-indol-3-yl)-*N*,*N*-dimethylethan-1-amine **4.6ae** which is an intermediate of biologically active Bufotinine[20] was synthesized by multistep reactions.[21] Gratifyingly, **4.6ae** was synthesized directly from indole and *N*,*N*-dimethylethanolamine in one step (63% yield).

4.2.3. Substrate scope for the synthesis of bis(indolyl)methane

Next, I was interested to examine the efficacy of catalyst **2.1A** toward the selective synthesis of bis(indolyl)methane. During the course of optimization reaction condition for the synthesis of C-3 alkylated indoles, it has been found that the 3,3'-(octane-1,1-diyl)bis(1H-indole) was obtained as major product when reaction was performed either in toluene or with the lower amount of alcohol (Table **4.1**, entries 1 & 9). Thus, when a mixture of indole (1 mmol), 1-octanol (0.5 mmol), KOH (0.25 mmol)

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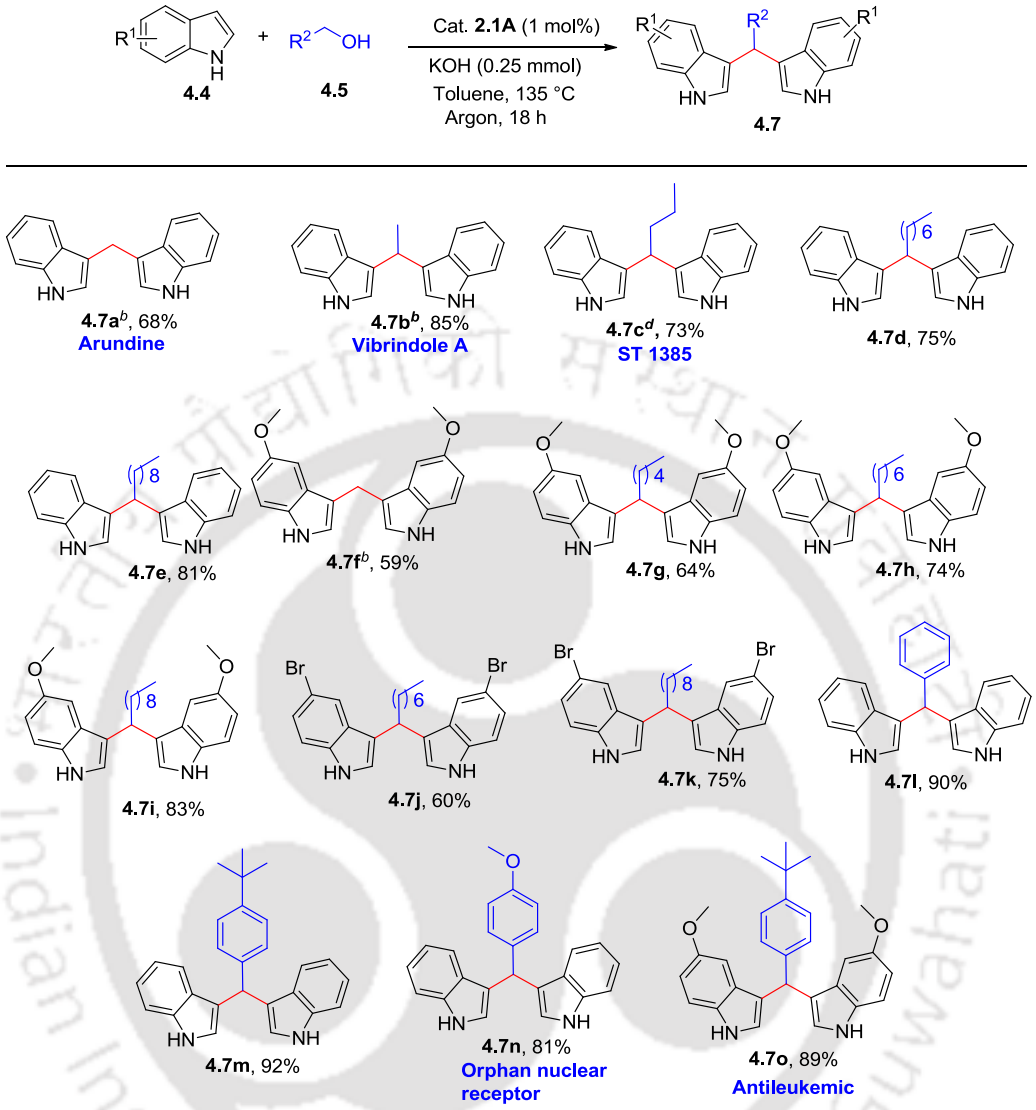

Scheme 4.12. Substrate scope for the synthesis of bis(indolyl)methane. [a] [a]Reaction conditions: indole (1 mmol), alcohol (0.5 mmol), cat. **2.1A** (0.005 mmol, 1 mol %), KOH (0.25 mmol), toluene (1 mL), 135 °C, 18 h. [b]0.5 mL MeOH, indole (2 mmol), KOH (1.5 mmol) toluene (1 mL), 100 mL Ace pressure tube. [c]0.5 mL EtOH, indole (2 mmol), toluene (1 mL), 100 mL Ace pressure tube. [d]0.5 mL BuOH, indole (2 mmol), toluene (1 mL), 100 mL Ace pressure tube.

and catalyst **2.1A** (1 mol %) were refluxed in toluene (1 mL) in an argon atmosphere for 18 h, 75% 3,3'-(octane-1,1-diyl)bis(1H-indole) **4.7d** was isolated. Further increasing the chain length of the alcohol yield was slightly increased to 81%. Next, I was interested to synthesize arundine (**4.7a**)[22] which is known as preventive for breast cancers. Arundine

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(**4.7a**) was isolated 68% yield by reacting indole with MeOH. This protocol also provides a route to synthesize vibrindole A (**4.7b**)[23] which is used to treat fibromyalgia and bowel syndrome in excellent yield (85%). Afterwards differently substituted indoles were reacted with wide range of aliphatic alcohols to obtain moderate to good yield of the corresponding product (**4.7c, 4.7e-4.7l**). Benzyl alcohols reacted well with indoles and structurally important[24] **4.7n** and **4.7o** were isolated in excellent yield (81% and 89% respectively) (Scheme **4.12**).

4.2.4. Optimization of reaction conditions of for the synthesis of C-3 alkylated indoles from 2-(2-nitrophenyl)ethan-1-ol and alcohols.

In order to utilize the liberated hydrogen molecule from dehydrogenation of alcohols, 2-(2-nitrophenyl)ethan-1-ol was used as a starting reagent to form indole. When, 2-(2-nitrophenyl)ethan-1-ol (0.5 mmol), KOH (5 mol %), catalyst **2.1A** (2 mol %) were refluxed at 135 $^{\circ}$C for 24 h in 15 mL Ace pressure tube, 17% indole was isolated. Inspired by this initial effort, the scope and limitation of this protocol have been studied toward the one-pot synthesis of C-3 alkylated indoles directly from 2-(2-nitrophenyl)ethan-1-ol and aliphatic alcohols. On initial trial, a mixture of 2-(2-nitrophenyl)ethan-1-ol (0.5 mmol) and 1-hexanol (1.5 mmol) was heated in an Ace pressure tube in the presence of catalyst **2.1A** (2 mol %) and KOH (0.5 mmol) for 48 h. The desired 3-hexyl-1H-indole **4.6d** was obtained in 20% yield (Table **4.2**, entry **1**). Interestingly, increasing amount of the alcohol (2.5 mmol), the yield of **4.6d** was enhanced to 40% (Table **4.2**, entry **2**).The yield of **4.6d** was further improved to 70% just by increasing the amount of the base (Table **4.2**, entry **3**). Here the excess base is required probably to assist the multiple oxidation and reduction steps. Then, the effect of different bases toward the progress of the reaction has been studied. It was established that bases like ^{t}BuOK, K_3PO_4, Cs_2CO_3 and K_2CO_3 proved incompetent for the betterment of the reaction (Table **4.2**, entries **5**, **7**, **8** & **9**).

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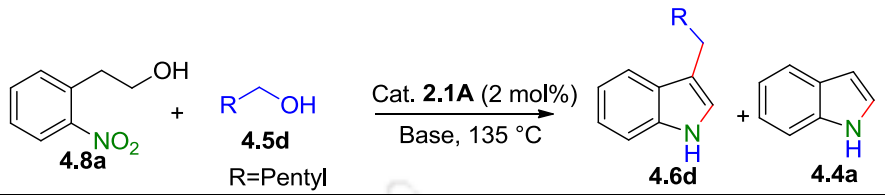
Table 4.2. Optimization of the reaction condition for the synthesis of C-3 alkylated indoles from 2-(2-nitrophenyl)ethan-1-ol and alcohols. [a]



Entry	**4.8a** (mmol)	**4.5d** (mmol)	Base (mmol)	Time (h)	**4.6d**[b]	**4.4a**[b]
1	0.5	1.5	KOH (0.5 mmol)	48	20	30
2	0.5	2.5	KOH (0.5 mmol)	48	40	10
3	0.5	2.5	KOH (1 mmol)	48	70	-
4	0.5	5	KOH (1 mmol)	48	50	-
5	0.5	2.5	^{t}BuOK (1 mmol)	48	30	-
6	0.5	2.5	KOH (1 mmol)	24	10	30
7	0.5	2.5	K_3PO_4 (1 mmol)	48	35	-
8	0.5	2.5	Cs_2CO_3 (1 mmol)	48	-	-
9	0.5	2.5	K_2CO_3 (1 mmol)	48	-	-

[a] Reaction conditions: 2-(2-nitrophenyl)ethan-1-ol (0.5 mmol), 1-hexanol (2.5 mmol), cat **2.1A** (0.01 mmol, 2 mol%) 15 mL Ace pressure tube, 135 °C, 48 h. [b] Isolated yield.

4.2.5. Substrate scope for the synthesis of C-3 alkylated indoles from 2-(2-nitrophenyl)ethan-1-ol and alcohols.

Next, the scope and limitation of the present protocol with respect to various aliphatic alcohols were examined (Scheme **4.13**). Various primary aliphatic alcohols responded well with 2-(2-nitrophenyl)ethan-1-ol providing moderate to good yield (40%-75%) (Scheme **4.13**, entries **4.6a-4.6n**). The reactions between substituted 2-(2-nitrophenyl)ethan-1-ol and other primary alcohols have also been studied. The representative substrates reacted well with methanol, 1-hexanol and 1-octanol, 1-decanol (Scheme **4.13**, entries **4.6bb-4.6hh**) under same conditions. Secondary alcohol like 2-octanol furnish desired product with 35% yield (**4.6h**).

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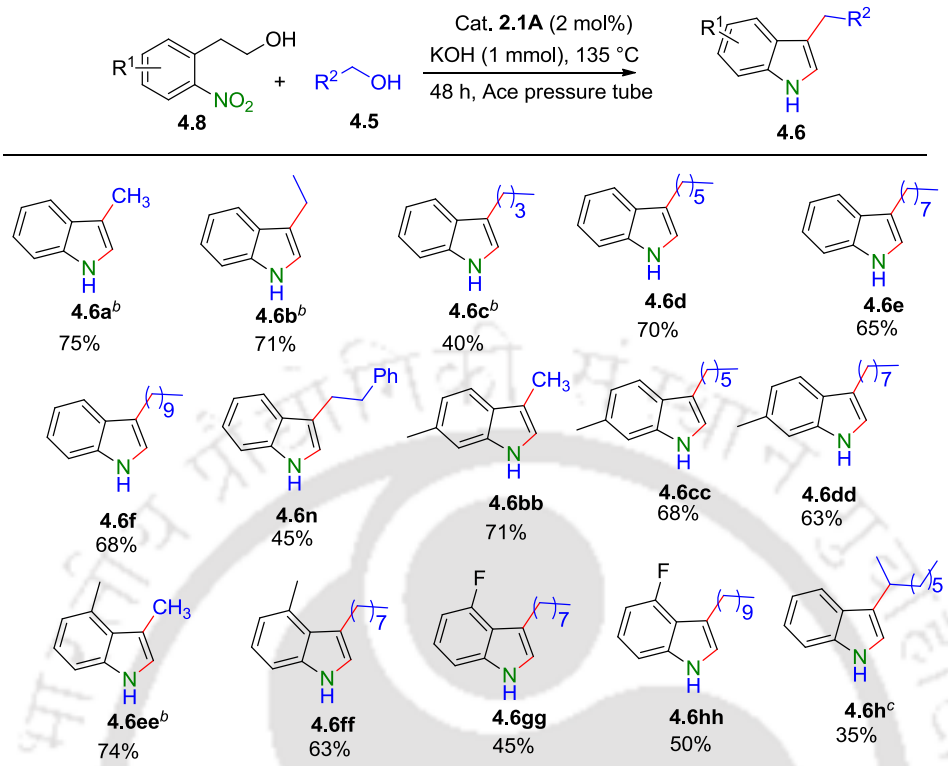
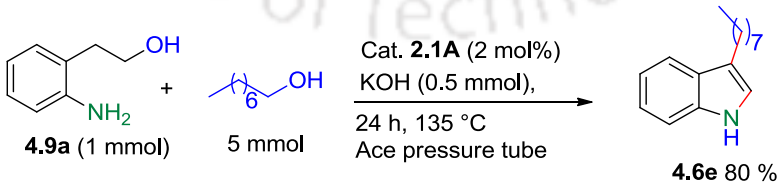


Scheme 4.13. Substrate scope for the synthesis of C-3 alkylated indoles from 2-(2-nitrophenyl)ethan-1-ol and alcohols.[a] [a]Reaction conditions: 2-(2-nitrophenyl)ethan-1-ol (0.5 mmol), alcohol (2.5 mmol), cat. **2.1A** (0.01 mmol, 2 mol %), KOH (1 mmol), 15 mL Ace pressure tube, 135 °C, 48 h. [b]1 mL alcohol. [c]72 h.

To prove that the reaction proceeds through in situ formation 2-(2-aminophenyl) acetaldehyde; 2-(2-aminophenyl)ethan-1-ol (4.9a) was reacted with octanol under the standard reaction conditions. Gratifyingly, the desired C-3 alkylated indole was isolated in good yield which indicate the involvement 2-(2-aminophenyl)ethan-1-ol as an intermediate in the reaction (Scheme **4.14**).



Scheme 4.14. C-3 alkylated indoles from 2-(2-aminophenyl)ethan-1-ol

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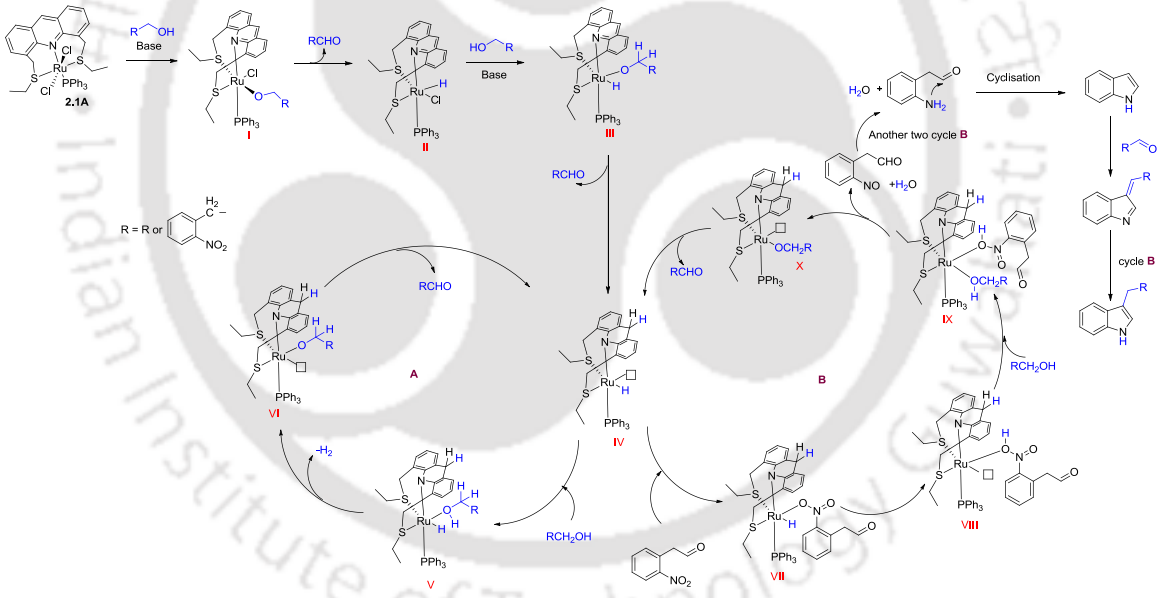
4.2.6. Plausible catalytic cycle:

We proposed a probable mechanism for the preparation of C-3 alkylated indoles from 2-(2-nitrophenyl)ethan-1-ol as shown in Scheme **4.15**. In the initial step, in presence of base and addition of alcohol, complex **2.1A** is converted ruthenium hydride species (**IV**) and the corresponding carbonyl compound. After that, alcohol coordination happened to the ruthenium centre and forms the complex **V**. After that removal of H_2 and aldehyde molecule, complex **IV** is regenerated and the cycle will continued. Complex **IV** reduces the -NO_2 group *via* -NO_2 coordination and insertion into the Ru-H bond and afforded 2-aminophenyl acetaldehyde. Then, cyclisation of 2-aminophenyl acetaldehyde involve indole formation. Then the reaction of indole with another molecule of aldehyde afforded C-3 alkylated indole.



Scheme 4.15. Plausible catalytic cycle

4.2.7. Competitive reactions

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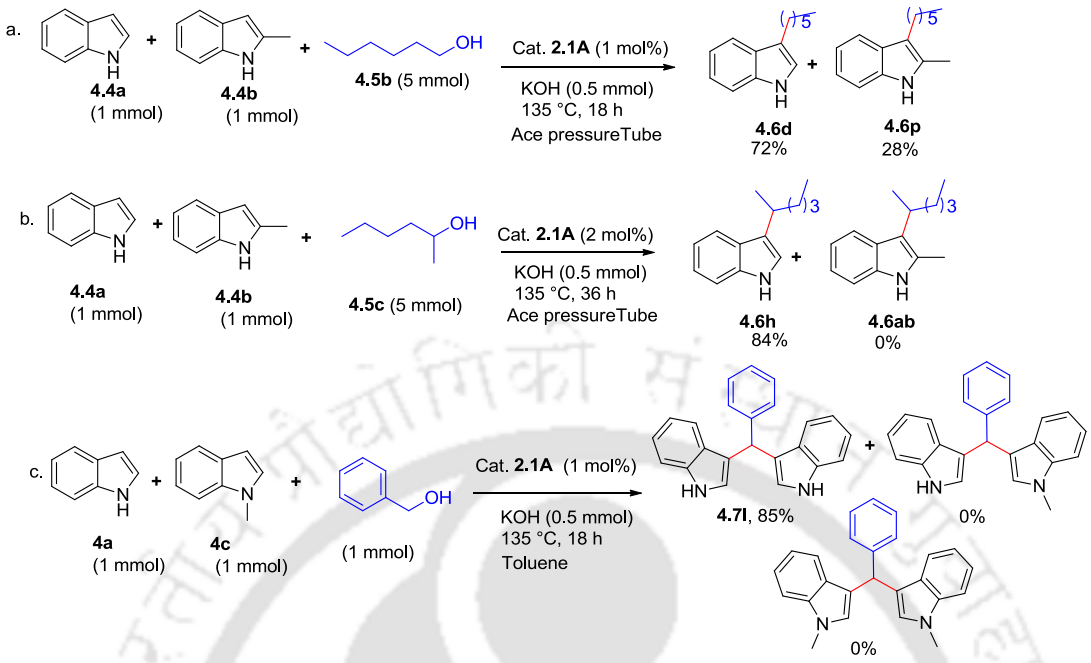

Scheme 4.16: Competitive reactions

Next, the reactivity and selectivity difference between indole and 2-substituted indole and primary and secondary alcohol were tested (Scheme **4.16**). When an equimolar mixture of indole and 2-methylindole (1 mmol) was reacted with 1-hexanol (5 mmol) in presence of 1 mol% cat **2.1A** and 0.5 mmol base, **4.6d** and **4.6p** were formed in a ratio of 72:28 after 18 h (Scheme **4.16**, **a**). Under the similar reaction conditions, when the equimolar mixture of indole and 2-methyl indole was reacted with secondary alcohol such as 2-hexanol, **4.6h** was obtained in 84% yield whereas no **4.6ab** was isolated (Scheme **4.16**, **b**). Thus, in the competitive C-alkylation, 2-methylindole reacts slower. Next, the scope of this protocol to synthesize unsymmetrical bis(indolyl)methanes[25] by reacting 1:1 mixture of indole and 1-methylindole with benzyl alcohol, but exclusively symmetrical bis(indolyl)methanes **4.7l** was isolated in 85% yield (Scheme **4.16**, **c**).

4.2.8. Control experiments:

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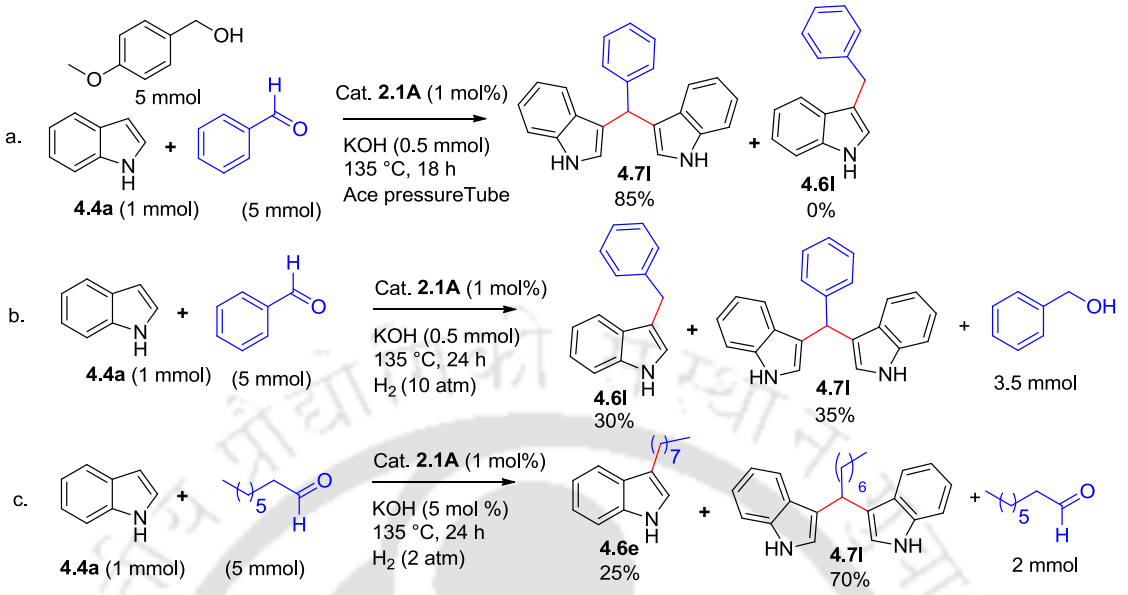

Scheme 4.17. Control experiments

To shed light on the proposed mechanistic pathway, some control experiments have been performed (Scheme **4.17**). During the synthesis of C-3 alkylated indole, the corresponding aldehyde is detected which indicates the dehydrogenation of the alcohol under the reaction conditions. Then, the hydrogenation step of α,β–unsaturated imine (vinylogous imine) was investigated. Thus, indole is reacted with a mixture of benzaldehyde and 4-methoxybenzyl alcohol under the optimized reaction condition, 3,3'-(phenylmethylene)bis(1H-indole) **4.7l** was obtained exclusively (85%) and no C-3 benzylated indole was observed (Scheme **4.17**, **a**). This suggests that the rate of formation of 3,3'-(phenylmethylene)bis(1H-indole) from indole and aldehyde is much faster than the dehydrogenation. Hence, vinylogous imine converted completely to the bis(indolyl)methane before the generation of a sufficient amount of H_2. Then, the reaction of indole with octanal/benzaldehyde under H_2 pressure was carried out (Scheme **4.17**, **b** & **c**), it was observed that the formation of C-3 alkylated indole together with bis(indolyl)methane (yield 32-35%) was formed and interestingly the hydrogenation of aldehyde to the corresponding alcohol (3 mmol) was also observed. These results suggest that the catalyst capable of dehydrogenating alcohol and also can hydrogenate aldehyde under H_2 pressure. In the C-3 alkylation reaction, the formed aldehyde is immediately

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captured by the indole to form vinylogous imine which is only available for hydrogenation to give the desired 3-alkylated indole. These results strongly allowed us to hypothesize that the slow generation of aldehyde and its coordination to the complex might be the key factor to get the good yield of the desired product in the C-3 alkylation reaction of indole.

4.3. Conclusion:

In summary, an acridine-derived air-stable ruthenium pincer complex catalyzed C-3 alkylation of indoles with alcohols was developed. A highly atom economical and environmentally benign "borrowing hydrogen" strategy was applied to activate a wide range of primary and secondary aliphatic alcohols for the synthesis of several C-3 alkylated indoles. Interestingly, just by tuning the reaction conditions, selectively bis(indolyl)methane scaffold constructed from the same set of alcohols and indoles. The present protocol is successfully applied to synthesize different structurally important compounds such as arundine, vibrindole A and tryptamine based alkaloid derivatives. Furthermore, the first ruthenium catalyzed one-pot synthesis of C-3 alkylated indole directly from 2-(2-nitrophenyl)ethan-1-ol and primary alcohol *via* sequential multistep reaction was demonstrated.

4.4. Experimental section:

4.4.1. General procedure: Unless otherwise mentioned, all chemicals were purchased from common commercial sources and used as received. $RuCl_2(PPh_3)_3$ was purchased from Sigma-Aldrich. All solvents were dried by standard procedure.[26] Solvents such as toluene were pre-dried using CaH_2 over Na with benzophenone indicator. The catalyst preparation was carried out under argon atmosphere with freshly distilled dry THF or dichloromethane. All catalytic reactions were carried out under argon atmosphere using dry glassware and standard syringe/septa techniques. DRX-400 Varian and Bruker Avance III 600 and 400 spectrometers were used to record ^{1}H, ^{13}C NMR and ^{31}P NMR, respectively. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane; spin-spin coupling constants (J) are expressed in Hz and other data are reported as

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follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, and br s = broad singlet. Column chromatography was done with SRL silica gel 100-200 mesh. Analytical thin layer chromatography (TLC) was carried out on silica gel plates (silica gel 60 F_{254}), that were visualized by exposure to ultraviolet light and an aqueous solution of p-anisaldehyde. The 2-Nitrophenylethyl alcohol/ substituted 2-Nitrophenylethyl alcohol were synthesized from 2-nitrotoluene/ substituted 2-nitrotoluene according to the literature procedure.[27]

4.4.2. General procedure for C-3 alkylation of indoles:

Indole (1 mmol), alcohol (5 mmol), complex **2.1A** (7.6 mg, 0.01 mmol) and KOH (28 mg, 0.5 mmol) were placed in a 30 mL Ace pressure tube under argon atmosphere. The tube was sealed with screw cap and then it was immersed in an oil bath at 135 °C and stirred at this temperature for 18 h. After that, the reaction mixture was cooled to room temperature, diluted with dichloromethane, and filtered over a plug of celite. The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (Hexane:Ethylacetate 50:1) on silica gel to afford the desired product.

4.4.3. General procedure for synthesis of bis(indolyl)methane from indoles and alcohols:

Indole (1 mmol), alcohol (0.5 mmol), complex **2.1A** (3.8 mg, 0.005 mmol), and KOH (14 mg, 0.25 mmol) were placed in a 2-neckd round bottom flask fitted with a coil condenser in argon atmosphere and added 1 mL toluene. Then, the reaction was refluxed for 18 h at 135 °C. After that, the reaction mixture was filtered through celite and the purification of the crude product was done by column chromatography using 10% ethylacetate in hexane.

4.4.4. General procedure for one-pot synthesis of substituted indoles from 2-(2-nitrophenyl)ethan-1-ol and alcohols:

2-(2-Nitrophenyl)ethan-1-ol (0.5 mmol), alcohol (2.5 mmol), complex **2.1A** (7.6 mg, 0.01), and KOH (28 mg, 0.5 mmol) were placed in a 15 mL Ace pressure tube under

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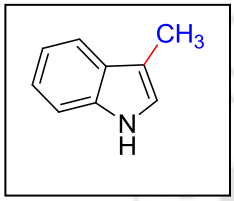
argon atmosphere. The tube was sealed with screw cap and then it was immersed in an oil bath at 135 °C and stirred at this temperature for 48 h. After that, the reaction mixture was cooled to room temperature, diluted with dichloromethane and filtered over a plug of celite. The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (Hexane:Ethylacetate 50:1).

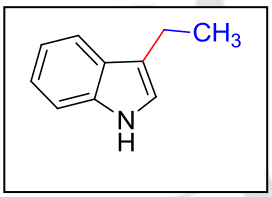
4.5. Characterization data of products:

3-Methyl-1H-indole (4.6a):[8i]



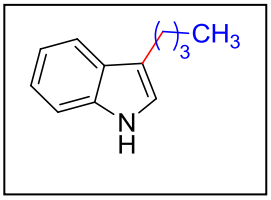
Pale yellow oil; Yield: 95% (0.125 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (br s, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.14-7.08 (m, 1H), 7.06-7.02 (m, 1H), 6.87 (m, 1H), 2.26 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.4, 128.4, 122.0, 121.7, 119.2, 118.9, 111.8, 111.1, 9.8.

3-Ethyl-1H-indole (4.6b):[28]



Light yellow oil; Yield: 78% (0.113 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (br s, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.27-7.23 (m, 1H), 7.20-7.16 (m, 1H), 7.01 (s, 1H), 2.86 (q, *J* = 7.5 Hz, 2H), 1.40 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.5, 127.5, 122.0, 120.6, 119.2, 119.1, 118.9, 111.1, 18.4, 14.6.

3-Butyl-1H-indole (4.6c):[16e]



Pale yellow oil; Yield: 60 % (0.103 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (brs, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.27-7.25 (m, 1H), 7.20-7.18 (m, 1H), 7.00 (s, 1H), 2.83 (t, *J* = 7.7 Hz, 2H), 1.80- 1.75 (m, 2H), 1.53-1.47 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.4, 127.7, 121.9, 121.1, 119.1, 117.2, 111.14, 32.5, 24.9, 22.8, 14.1.

3-Hexyl-1H-indole (4.6d):[16e]

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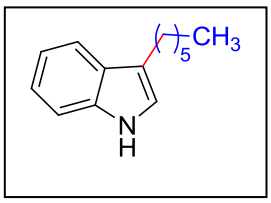
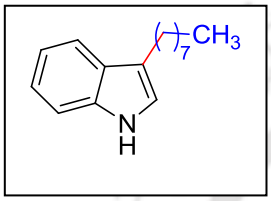


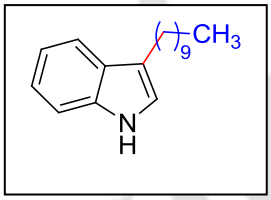
Pale yellow oil; Yield: 87 % (0.174 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.23-7.13 (m, 2H), 7.00-6.99 (m, 1H), 2.79 (t, *J* = 7.7 Hz, 2H), 1.77-1.72 (m, 2H), 1.44-1.34 (m, 6H), 0.93 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.4, 127.7, 121.9, 121.1, 119.1, 117.3, 111.1, 31.9, 30.3, 29.5, 25.3, 22.8, 14.3.

3-Octyl-1H-indole (4.6e):[16e]



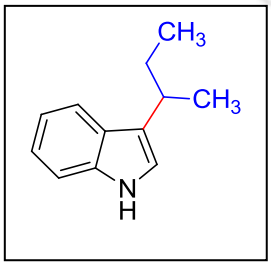
Yellow oil; Yield: 85 % (0.194 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (br s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.00 (br s, 1H), 2.79 (t, *J* = 7.7 Hz, 2H), 1.78-1.73 (m, 2H), 1.47-1.30 (m, 10H), 0.93 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.4, 127.7, 121.9, 121.1, 119.1, 117.3, 111.1, 32.1, 30.3, 29.8, 29.7, 29.5, 25.3, 22.8, 14.3.

3-Decyl-1H-indole (4.6f):[29]



Pale yellow oil; Yield: 80 % (0.205 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.00-6.99 (m, 1H), 2.77 (t, *J* = 8.4, 2H), 1.76-1.71 (m, 2H), 1.44-1.29 (m, 14H), 0.91 (t, *J* = 4.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.4, 127.7, 121.9, 121.1, 119.1, 117.3, 111.1, 32.1, 30.3, 29.8, 29.8, 29.7, 29.5, 25.3, 22.8, 14.3. several peaks are eclipsed.

3-(Sec-butyl)-1H-indole (4.6g):[30]



Pale yellow oil; Yield: 80 % (0.138 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (br s, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.23-7.20 (m, 1H), 7.16-7.13 (m, 1H), 6.98 (d, *J* = 2.3 Hz, 1H), 3.03-3.00 (m, 1H), 1.90-1.83 (m, 1H), 1.74-1.67 (m, 1H), 1.39 (d, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.6, 127.1, 122.7, 121.8, 120.0, 119.5, 119.0, 111.2, 32.6, 30.4, 20.98, 12.3.

3-(Sec-octyl)-1H-indole (4.6h):[31]

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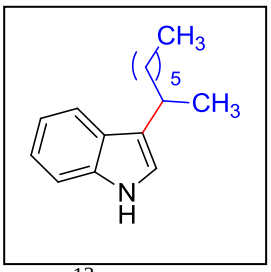
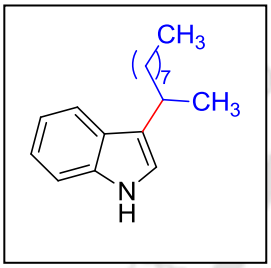


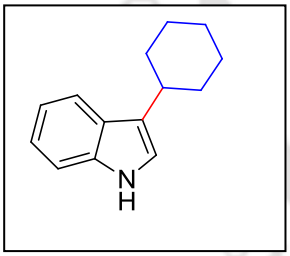
Pale yellow oil; Yield: 88 % (0.201 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.21-7.18 (m, 1H), 7.13-7.11 (m, 1H), 6.98 (d, *J* = 2.3 Hz, 1H), 3.08-3.02 (m, 1H), 1.83-1.78 (m, 1H), 1.65-1.59 (m, 1H), 1.36 (d, *J* = 6.9 Hz, 3H), 1.34-1.25 (m, 8H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.6, 127.0, 123.0, 121.8, 119.9, 119.6, 119.0, 111.2, 37.8, 32.0, 30.9, 29.6, 27.8, 22.8, 21.5, 14.3.

3-(Sec-decyl)-1H-indole (4.4.6i):[32]



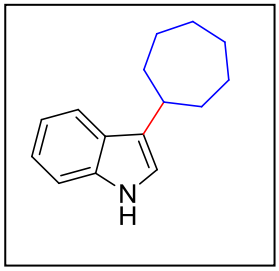
Pale yellow oil; Yield: 84 % (0.215 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.23-7.20 (m, 1H), 7.15-7.12 (m, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 3.09-3.03 (m, 1H), 1.84-1.79 (m, 1H), 1.67-1.61 (m, 1H), 1.38 (d, *J* = 7.0 Hz, 3H), 1.36-1.25 (m, 12H), 0.91 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.6, 127.0, 123.0, 121.85, 119.9, 119.6, 119.0, 111.2, 37.8, 32.0, 30.9, 30.0, 29.8, 29.5, 27.9, 22.8, 21.5, 14.3.

3-Cyclohexyl-1H-indole (4.6j):[33]



Yellow oil; Yield: 67 % (0.133 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (br s, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.19-7.16 (m, 1H), 7.11-7.09 (m, 1H), 6.95 (d, *J*= 2 Hz, 1H), 2.86-2.82 (m, 1H), 2.12-2.10 (m, 2H), 1.86-1.84 (m, 2H), 1.52-1.43 (m, 4H), 1.33-1.26 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.5, 126.9, 123.4, 121.9, 119.5 (2C), 119.1, 111.2, 35.5, 34.17, 27.1, 26.7.

3-Cycloheptyl-1H-indole (4.6k):[34]



Light yellow oil; Yield: 70 % (0.149 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (br s, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.26-7.23 (m, 1H), 7.19-7.16 (m, 1H), 6.98 (d, *J* = 2.3 Hz, 1H), 3.14-3.08 (m, 1H), 2.19-2.16 (m, 2H), 1.87-1.53 (m, 10H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.5, 126.7, 124.4, 121.8, 119.4, 119.4, 119.0, 111.2, 37.4, 35.8, 28.4, 27.1.

3-Benzyl-1H-indole (4.6l):[16e]

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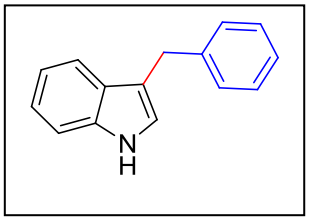
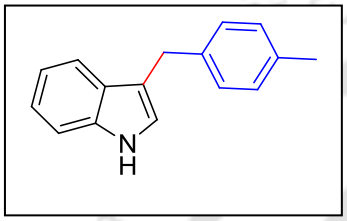


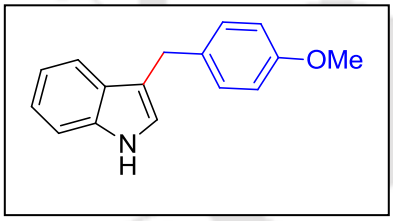
White solid; Yield: 60 % (0.124 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (br s, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.37-7.33 (m, 4H), 7.28-7.25 (m, 2H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.94 (br s, 1H), 4.19 (s, 2H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.3, 136.5, 128.8, 128.4, 127.5, 126.0, 122.46, 122.1, 119.4, 119.2, 115.8, 111.2, 31.7.

3-(4-Methylbenzyl)-1H-indole (4.6l$_1$):[15]



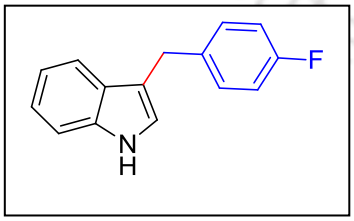
Light yellow solid; Yield: 62 % (0.137 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.24-7.21 (m, 3H), 7.13-7.11 (m, 3H), 6.94 (br s, 1H), 4.12 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.3, 136.6, 135.4, 129.1, 128.7, 127.6, 122.4, 122.1, 119.5, 119.3, 116.3, 111.1, 31.3, 21.1.

3-(4-Methoxybenzyl)-1H-indole (4.6l$_2$):[16e]



Off white solid; Yield: 58 % (0.137 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.28-7.24 (m, 3H), 7.17-7.14 (m, 1H), 6.92-6.91 (m, 1H), 6.91-6.89 (m, 2H), 4.13 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.9, 136.6, 133.4, 129.7, 127.5, 122.3, 122.1, 119.4, 119.3, 116.3, 113.9, 111.2, 55.3, 30.8.

3-(4-Fluorobenzyl)-1H-indole (4.6l$_3$):[35]



Light yellow solid; Yield: 55 % (0.123 g);^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (br s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.28-7.22 (m, 3H), 7.13-7.11 (m, 1H), 6.99 (t, *J*=8.7 Hz, 2H), 6.94 (br s, 1H), 4.12 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 161.4 (d, *J* = 243.3 Hz), 136.9 (d, *J* = 3.0 Hz), 136.6, 130.1 (d, *J* = 7.8 Hz), 127.4, 122.4, 122.3, 119.5, 119.2, 115.8, 115.2 (d, *J* = 21.2 Hz), 111.2, 30.9.

3-(Thiophen-2-ylmethyl)-1H-indole (4.6m):[16e]

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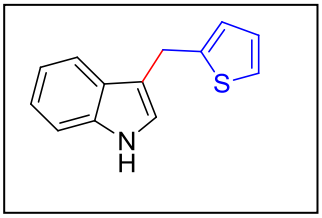
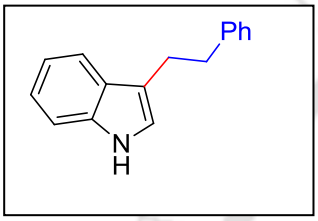


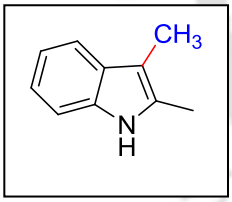
Light yellow solid; Yield:72 % (0.153 g);[1]H NMR (600 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.16-7.12 (m, 2H), 7.08-7.07 (m, 1H), 6.95-6.94 (m, 1H), 6.91-6.90 (m, 1H), 4.35 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.7, 136.4, 127.2, 126.8, 124.8, 123.5, 122.3, 122.3, 119.6, 119.1, 115.4, 111.2, 26.0.

***3-Phenethyl-1H-indole (4.6n)*:**[15]



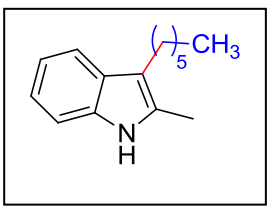
Light yellow solid; Yield: 75 % (0.165 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.35-7.32 (m, 2H), 7.29-7.23 (m, 4H), 7.19-7.16 (m, 1H), 6.96 (br s, 1H), 3.13-3.07 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.5, 136.4, 128.6, 128.4, 127.55, 125.9, 122.1, 121.4, 119.3, 119.0, 116.3, 111.2, 36.6, 27.4.

***2,3-Dimethyl-1H-indole (4.6o)*:**[8i]



Light yellow oil; Yield: 80 % (0.126 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (br s, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 6.8 Hz, 1H), 7.15-7.09 (m, 2H), 2.39 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.2, 130.7, 129.5, 121.0, 119.1, 118.0, 110.1, 107.2, 11.7, 8.6.

***2-Methyl-3-hexyl-1H-indole (4.6p)*:**[16e]



Light yellow oil; Yield: 66 % (0.141 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (br s, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.29-7.28 (m, 1H), 7.14-7.08 (m, 2H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.39 (s, 3H), 1.65-1.61 (m, 2H), 1.39-1.36 (m, 2H), 1.35-1.30 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.3, 130.7, 128.9, 120.8, 119.0, 118.3, 112.6, 110.2, 32.0, 30.9, 29.4, 24.2, 22.9, 14.3, 11.8.

***2-Methyl-3-octyl-1H-indole (4.6q)*:**[12]

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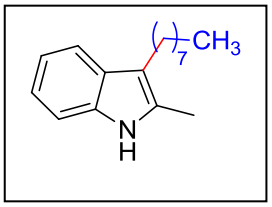
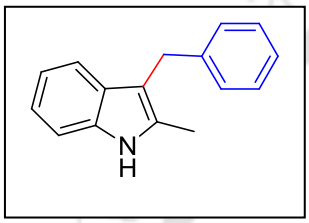


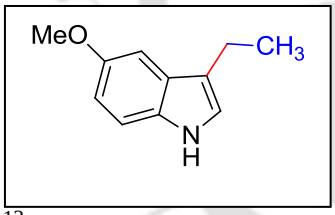
Light yellow oil; Yield: 69 % (0.167 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (br s, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.17-7.15 (m, 1H), 7.04-6.96 (m, 2H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.27 (s, 3H), 1.57-1.47 (m, 2H), 1.24-1.18 (m, 10H), 0.80 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.3, 130.6, 128.9, 120.8, 119.0, 118.3, 112.6, 110.2, 32.1, 30.9, 29.8, 29.7, 29.5, 24.3, 22.8, 14.2, 11.8.

2-Methyl-3-benzyl-1H-indole (4.6r):[36]



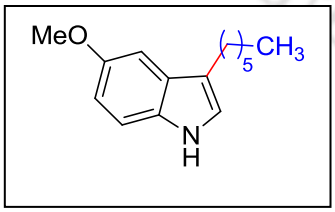
Light yellow solid; Yield: 75 % (0.165 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.31-7.24 (m, 5H), 7.19-7.17 (m, 1H), 7.15-7.12 (m, 1H), 7.14-7.07 (m, 1H), 4.10 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.7, 135.4, 131.7, 129.0, 128.4, 128.4, 125.8, 121.1, 119.3, 118.5, 110.7, 110.2, 30.2, 11.9.

5-Methoxy-3-ethyl-1H-indole (4.6s):[8k]



Light yellow oil; Yield: 89 % (0.155 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.27 (d, *J* = 8.7 Hz, 1H), 7.10-7.09 (m, 1H), 6.99 (br s, 1H), 6.91(dd, *J*= 8.7, 2.5 Hz, 1H), 3.92 (s, 3H), 2.80 (q, *J* = 7.5 Hz, 2H), 1.38 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.9, 131.8, 127.8, 121.5, 118.6, 112.1, 111.9, 100.9, 56.1, 18.4, 14.4.

5-Methoxy-3-hexyl-1H-indole (4.6t):[16e]



Light yellow oil; Yield: 85 % (0.196 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 7.08 (d, *J* = 2.5 Hz, 1H), 6.98 (br s, 1H), 6.88 (dd, *J* = 8.7, 2.4 Hz, 1H), 3.91 (s, 3H), 2.74 (t , *J* = 7.6 Hz, 2H), 1.76-1.71 (m, 2H), 1.46-1.42 (m, 2H), 1.38-1.34 (m, 4H), 0.93 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.8, 131.6, 128.1, 122.0, 117.0, 112.0, 111.8, 101.0, 56.1, 31.9, 30.1, 29.5, 25.3, 22.8, 14.3.

5-Methoxy-3-otyl-1H-indole (4.6u):[36]

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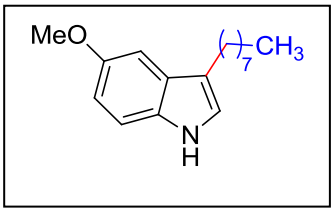
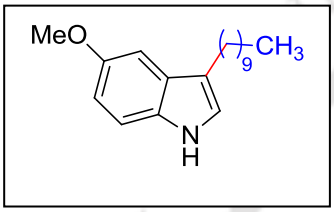


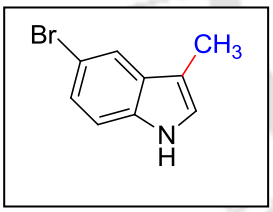
Light yellow oil; Yield: 82 % (0.212 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 7.06 (d, *J* = 2.5 Hz, 1H), 6.98 (br s, 1H), 6.87 (dd, *J*= 8.8, 2.5 Hz, 1H), 3.90 (s, 3H), 2.73 (t, *J* = 7.7 Hz, 2H), 1.74-1.71 (m, 2H), 1.43-1.40 (m, 2H), 1.38-1.28 (m, 8H), 0.90 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.6, 131.9, 127.7, 122.3, 120.3, 111.8, 111.7, 102.0, 56.0, 35.6, 34.1, 32.1, 29.9, 29.5, 28.4, 22.8, 14.2.

5-Methoxy-3-decyl-1H-indole (4.6v):



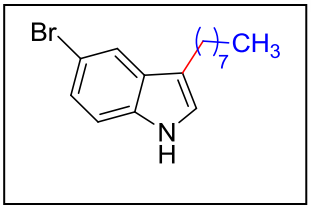
Light yellow oil; Yield: 79 % (0.226 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 7.06 (d, *J* = 2.5 Hz, 1H), 6.98 (br s, 1H), 6.87(dd, *J*= 8.7, 2.5 Hz, 1H), 3.90 (s, 3H), 2.73 (t, *J* = 7.7 Hz, 2H), 1.74-1.69 (m, 2H), 1.44-1.28 (m, 14H), 0.90 (t, *J* = 7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.75, 131.51, 128.00, 121.88, 116.95, 111.91, 111.69, 100.95, 55.98, 31.94, 30.02, 29.72, 29.70, 29.60, 29.39, 26.91, 25.18, 22.72, 14.16; HRMS (ESI+): *m/z* calcd. for $C_{19}H_{30}NO$:288.2327 $[M+H]^+$; Found 288.2337.

***5-Bromo-3-methyl-1H-indole (4.6w)*:**[8j]



Light yellow oil; Yield: 58 % (0.121 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.74 (s, 1H), 7.30-7.23 (m, 2H), 7.00 (br s, 1H), 2.32 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 134.9, 130.20, 124.7, 122.9, 121.6, 112.5 (2C), 111.6, 9.7.

5-Bromo-3-octyl-1H-indole (4.6x):



Light yellow oil; Yield: 52 % (0.160 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (br s, 1H), 7.75 (s, 1H), 7.29-7.23 (m, 2H), 7.00 (d, *J* = 2.3 Hz, 1H), 2.71 (t, *J* = 7.7 Hz, 2H), 1.72-1.67 (m, 2H), 1.43-1.27 (m, 10H), 0.91 (t, *J* = 6.9 Hz, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.0, 129.6, 124.7, 122.4, 121.8, 117.1, 112.6, 112.5, 32.0, 30.2, 29.74, 29.6, 29.5, 25.1, 22.8, 14.3. HRMS (ESI+): *m/z* calcd. for $C_{16}H_{23}BrN$: 308.1014 $[M+H]^+$; Found: 308.1021.

3-(Sec-butyl)-5-methoxy-1H-indole (4.6y):

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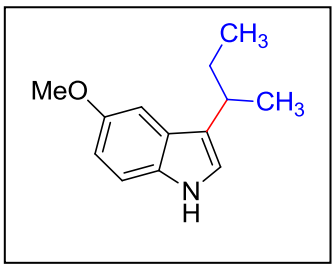
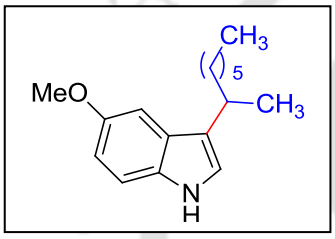


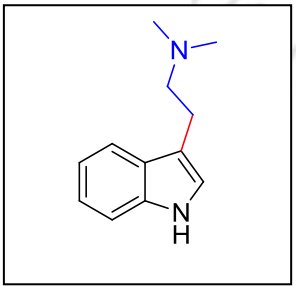
Light yellow oil; Yield: 70 % (0.142 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.27 (d, *J* = 8.7 Hz, 1H), 7.14 (d, *J* = 2.4 Hz, 1H), 6.96 (d, *J* = 2.3 Hz, 1H), 6.90 (dd, *J*=8.8, 2.4 Hz, 1H), 3.92 (s, 3H), 3.00-2.94 (m, 1H), 1.89-1.83 (m, 1H), 1.73-1.66 (m, 1H), 1.38 (d, *J* = 6.9 Hz, 3H), 0.97 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.6, 131.8, 127.4, 122.3, 121.0, 111.9, 111.8, 101.6, 56.1, 32.5, 30.3, 20.8, 12.3. HRMS (ESI+): *m/z* calcd. for $C_{13}H_{18}NO$: 204.1388 $[M+H]^+$; found: 204.1388.

3-(Sec-octyl)-5-methoxy-1H-indole (4.6z):



Light yellow oil; Yield: 76 % (0.196 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.27 (d, *J* = 8.7 Hz, 1H), 7.13 (s, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.90-6.88 (m, 1H), 3.92 (s, 3H), 3.04-3.00 (m, 1H), 1.84-1.78 (m, 1H), 1.66-1.61 (m, 1H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.35-1.28 (m, 8H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.6, 131.8, 127.4, 122.7, 120.8, 111.8, 111.8, 101.6, 56.1, 37.7, 32.0, 30.8, 29.6, 27.8, 22.8, 21.4, 14.27. HRMS (ESI+): *m/z* calcd. for $C_{17}H_{26}NO$: 260.2014 $[M+H]^+$, Found: 260.2013.

2-(1H-indol-3-yl)-N,N-dimethylethan-1-amine (4.6ad):[37]



Light yellow oil; Yield: 65 % (0.122 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (br s, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.23-7.14 (m, 2H), 6.99 (br s, 1H), 3.00 (t, *J* = 7.8 Hz, 2H), 2.72 (t, *J* = 7.8 Hz, 2H), 2.40 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.4, 127.5, 121.9, 121.7, 119.2, 118.8, 114.0, 111.3, 60.3, 45.4, 23.6.

2-(5-Methoxy-1H-indol-3-yl)-N,N-dimethylethan-1-amine (4.6ae):[38]

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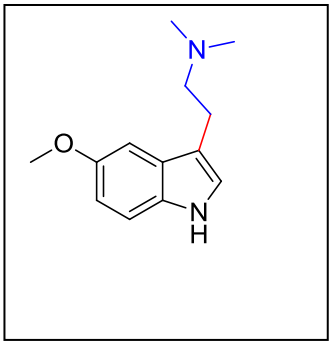
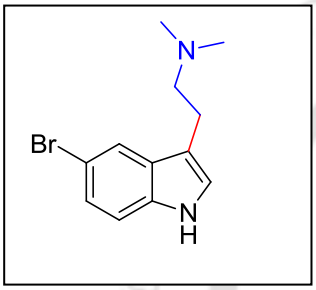


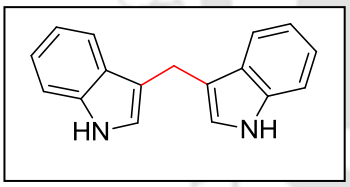
Light yellow oil; Yield: 63 % (0.137 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (br s, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.07 (d, *J* = 2.5 Hz, 1H), 6.96 (br s, 1H), 6.87 (dd, J=8.8, 2.5 Hz, 1H), 3.88 (s, 3H), 2.95 (t, *J* = 7.8 Hz, 2H), 2.68 (t, *J* = 7.8 Hz, 2H), 2.39 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.9, 131.7, 127.9, 122.6, 122.6, 113.8, 112.0, 112.0, 100.8, 60.2, 56.1, 45.4.

2-(5-Bromo-1H-indol-3-yl)-N,N-dimethylethan-1-amine (4.6af):[39]



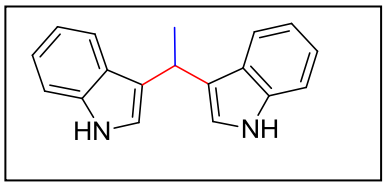
Light yellow oil; Yield: 40 % (0.106 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (br s, 1H), 7.74-7.01 (4H), 2.93 (t, *J* = 7.8 Hz, 2H), 2.67 (t, *J* = 7.4 Hz, 2H), 2.39 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.1, 129.4, 124.8, 123.0, 122.1, 121.5, 119.3, 112.7, 111.3, 60.3, 45.4, 23.5. (From NMR **6af**:**6ad**::60:40)

Arundine or Di(1H-indol-3-yl)methane (4.7a):[40]



White solid; Yield: 68% (0.0837 g); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.91 (br, s, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.22 (t, *J* = 7.2 Hz , 2H), 7.13 (t, *J* = 7.2 Hz, 2H), 6.96-6.95 (m, 2H), 4.28 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 136.6, 127.7, 122.3, 122.0, 119.3, 119.3, 115.8, 111.1, 21.3.

Vibrindole A or Di(1H-indol-3-yl)ethane (4.7b): [23c]



White solid; Yield: 85% (0.110 g); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 (br s, 2H), 7.61 (d, *J* = 7.9 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.20 (t, *J* = 7.14 Hz, 2H), 7.08 (t, *J* = 7.5 Hz, 2H), 6.95 (d, *J* = 1.5 Hz, 2H) , 4.71 (q, *J* = 7.2 Hz, 1H), 1.84 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, 150 MHz) δ 136.7, 127.0, 121.9, 121.8, 121.3, 119.8, 119.1, 111.2, 28.3, 21.8.

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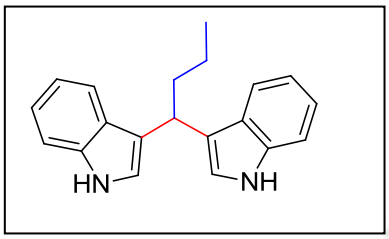
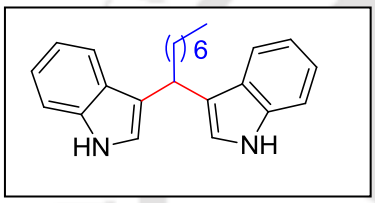
ST 1385 or Di(1H-indol-3-yl)butane (4.7c):[41]



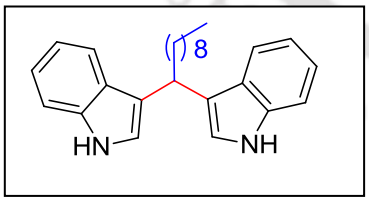
Orange solid; Yield: 73% (0.105 g); ^{1}H NMR (600 MHz, $CDCl_3$)δ 7.86 (br s, 2H), 7.65 (d, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.21 (t, *J* = 7.1 Hz, 2H), 7.08 (t, *J* = 7.1 Hz, 2H), 6.99 (d, *J* = 2.4 Hz, 2H), 4.54 (t, *J* = 7.4 Hz, 1H), 2.26-2.22 (m, 2H), 1.51-1.45 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.6, 127.3, 121.8, 121.5, 120.6, 119.8, 119.1, 111.1, 38.2, 33.8, 21.5, 14.3.

3,3'-(Octane-1,1-diyl)bis(1H-indole) (4.7d):[42]



Colorless solid; Yield: 75% (0.129 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.93 (br s, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.17 (t, *J* = 8.1 Hz, 2H), 7.06 (t, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 2.4 Hz, 2H), 4.50 (t, *J* = 7.4 Hz, 1H), 2.26-2.22 (m, 2H) , 1.45-1.41 (m, 2H), 1.39-1.34 (m, 2H), 1.30-1.23 (m, 6H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.7, 127.3, 121.8, 121.5, 120.7, 119.8, 119.1, 111.1, 35.9, 34.1, 32.1, 29.9, 29.5, 28.5, 22.8, 14.2.

3,3'-(Decane-1,1-diyl)bis(1H-indole) (4.7e):[43]



Black oil; Yield: 81% (0.151 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (br s, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 2H), 7.01 (d, *J* = 2.3 Hz, 2H), 4.50 (t, *J* = 7.4 Hz, 1H), 2.26-2.22 (m, 2H), 1.46-1.42 (m, 2H), 1.39-1.35 (m, 2H), 1.32-1.24 (m, 10H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.7, 127.3, 121.8, 121.5, 120.7, 119.8, 119.1, 111.1, 36.0, 34.1, 32.0, 29.9, 29.8, 29.8, 29.5, 28.5, 22.8, 14.3.

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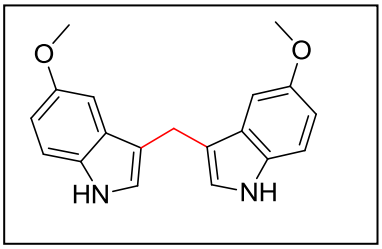
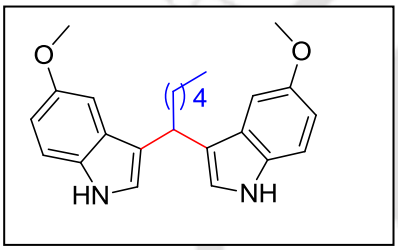
Bis(5-methoxy-1H-indol-3-yl)methane (4.7f):[41]



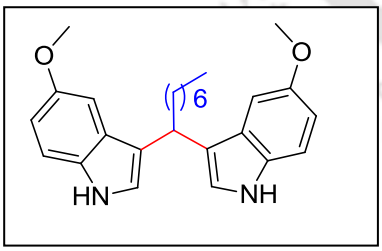
Red solid; Yield: 59% (0.090 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (br s, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 2.5 Hz, 2H), 6.92 (br s, 2H), 6.86 (dd, *J* = 8.8, 2.5 Hz, 2H), 4.17 (s, 2H), 3.82 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.9, 131.7, 128.0, 123.2, 115.4, 112.2, 111.9, 101.1, 56.0, 21.4.

3,3'-(Hexane-1,1-diyl)bis(5-methoxy-1H-indole) (4.7g):



Yellow solid; Yield: 64% (0.120 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (br s, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 2.5 Hz, 2H), 6.98 (d, *J* = 2.5 Hz, 2H), 6.81 (dd, *J* = 8.7, 2.5 Hz, 2H), 4.36 (t, *J* = 7.4 Hz, 1H), 3.78 (s, 6H), 2.21-2.17 (m, 2H), 1.44-1.40 (m, 2H), 1.37-1.32 (m, 2H), 1.31-1.25(m, 2H),0.85 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.6, 131.9, 127.7, 122.3, 120.3, 111.7, 111.7, 102.0, 56.0, 35.6, 34.1, 32.1, 28.1, 22.8, 14.3. HRMS (ESI+): *m/z* calcd. for $C_{24}H_{29}N_2O_2$: 377.2229 $[M+H]^+$; found: 377.2238.

3,3'-(Octane-1,1-diyl)bis(5-methoxy-1H-indole) (4.7h).



Yellow solid; Yield: 74% (0.150 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (br s, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 2.5 Hz, 2H), 6.99 (d, *J* = 2.4 Hz, 2H), 6.81 (dd, *J* = 8.8, 2.5 Hz, 2H), 4.36 (t, *J* = 7.4 Hz, 1H), 3.78 (s, 6H), 2.21-2.17 (m, 2H), 1.44-1.39 (m, 2H), 1.38-1.34 (m, 2H), 1.28-1.22 (m, 6H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.6, 131.9, 127.7, 122.4, 120.3, 111.8, 111.6, 102.0, 56.0, 35.6, 34.1, 32.1, 29.9, 29.5, 28.4, 22.8, 14.2. HRMS (ESI+): *m/z* calcd. for $C_{26}H_{33}N_2O_2$: 405.2542 $[M+H]^+$; found: 405.2546.

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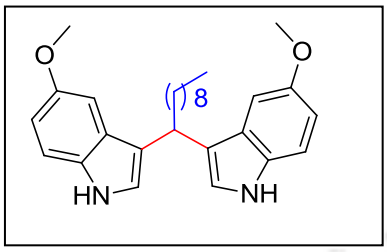
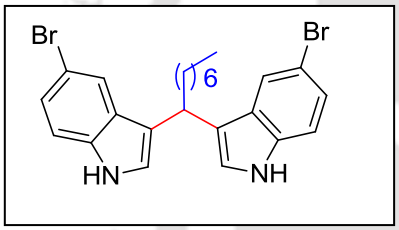
3,3'-(Decane-1,1-diyl)bis(5-methoxy-1H-indole) (4.7i).



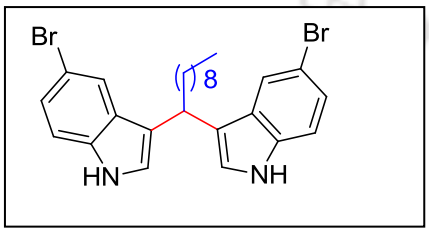
Pale yellow solid; Yield: 83% (0.179 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (br s, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 2.5 Hz, 2H), 6.98 (d, *J* = 2.4 Hz, 2H), 6.81 (dd, *J* = 8.8, 2.5 Hz, 2H), 4.36 (t, *J* = 7.4 Hz, 1H), 3.78 (s, 6H), 2.21-2.17 (m, 2H), 1.44-1.40 (m, 2H), 1.37-1.33 (m, 2H), 1.28-1.23 (m, 10H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.6, 131.9, 127.7, 122.3, 120.3, 111.8, 111.7, 102.0, 56.0, 35.6, 34.1, 32.0, 29.9, 29.8, 29.8, 29.5, 28.4, 22.8, 14.3. HRMS (ESI+): *m/z* calcd. for $C_{28}H_{37}N_2O_2$: 433.2855 $[M+H]^+$; found: 433.2851.

3,3'-(Octane-1,1-diyl)bis(5-bromo-1H-indole) (4.7j):[44]



Brown solid; Yield: 60% (0.150 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (br s, 2H), 7.65 (d, *J* = 1.6 Hz, 2H), 7.26-7.21 (m, 4H), 7.05 (d, *J* = 1.9 Hz, 2H), 4.32 (t, *J* = 7.5 Hz, 1H), 2.17-2.13 (m, 2H), 1.38-1.21 (m, 10H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.4, 128.8, 124.8, 122.7, 122.2, 119.8, 112.7, 112.5, 35.4, 34.1, 32.0, 29.7, 29.4, 28.35, 22.8, 14.2.

3,3'-(Decane-1,1-diyl)bis(5-bromo-1H-indole) (4.7k):



Brown solid; Yield: 75% (0.199 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (br s, 2H), 7.65 (d, *J* = 1.7 Hz, 2H), 7.23-7.17 (m, 4H), 7.03 (d, *J* = 2.4 Hz, 2H), 4.32 (t, *J* = 7.5 Hz, 1H), 2.17-2.13 (m, 2H), 1.36-1.32 (m, 4H), 1.29-1.21(m, 10H) 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.4, 128.8, 124.8, 122.7, 122.2, 119.8, 112.7, 112.5, 35.4, 34.1, 32.0, 29.7, 29.7, 29.5, 28.3, 22.8, 14.3. One peak eclipsed HRMS (ESI+): *m/z* calcd. for $C_{26}H_{31}Br_2N_2$: 531.0834$[M+H]^+$; found: 531.0829.

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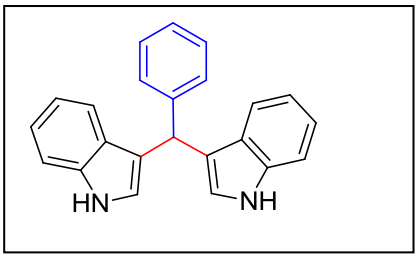
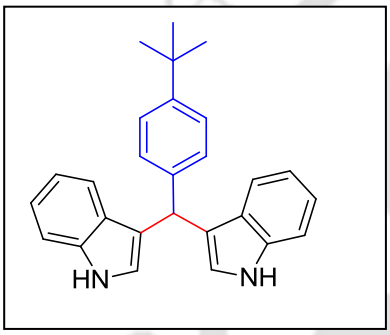
3,3'-(Phenylmethylene)bis(1H-indole) (4.7l):[24]



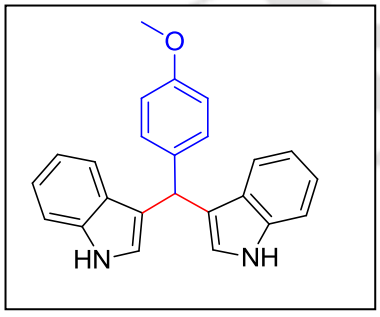
Red solid; Yield: 90% (0.145 g);^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (br s, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.36-7.34 (m, 4H), 7.28 (t, *J*= 7.6 Hz, 2H), 7.22-7.15 (m, 3H), 7.00 (t, *J*= 7.3 Hz, 2H), 6.66 (d, *J* = 2.4 Hz, 2H), 5.89 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.1, 136.8, 128.8, 128.3, 127.2, 126.2, 123.7, 122.0, 120.1, 119.8, 119.3, 111.1, 40.3.

3,3'-((4-(Tert-butyl)phenyl)methylene)bis(1H-indole) (4.7m):[45]



Orange Solid; Yield: 92% (0.174 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (br s, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.32-7.26 (m, 4H), 7.19 (t, *J* = 7.8 Hz, 2H), 7.03 (t, *J* = 7.8 Hz, 2H), 6.66 (d, *J* = 2.4 Hz, 2H), 5.85 (s, 1H), 1.29 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.8, 140.9, 136.8, 128.3, 127.2, 125.1, 123.7, 122.0, 120.1, 120.1, 119.2, 111.1, 39.7, 34.5, 31.6.

3,3'-((4-Methoxyphenyl)methylene)bis(1H-indole) (4.7n):[24]



Solid; Yield: 81% (0.143 g); ^{1}H NMR (600 MHz, $CDCl_3$)δ 7.93 (br s, 2H), 7.39 (d, *J* = 7.9 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J*=7.6, 2H), 7.17 (t, *J* = 7.4 Hz, 2H), 7.00 (t, *J* = 7.5 Hz, 2H), 6.82 (d, *J*=8.7 Hz, 2H), 6.67 (d, *J* = 2.4 Hz, 2H), 5.84 (s, 1H), 3.78 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.0, 136.8, 136.3, 129.7, 127.2, 123.6, 122.0, 120.2, 120.1, 119.3, 113.7, 111.1, 55.3, 39.5.

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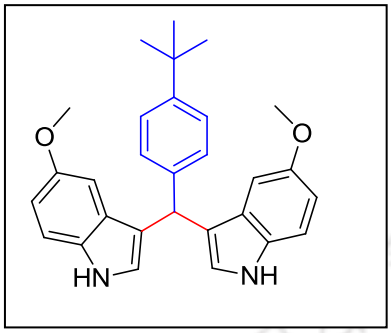
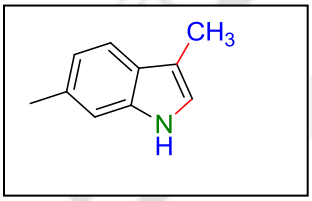
3,3'-((4-(Tert-butyl)phenyl)methylene)bis(5-methoxy-1H-indole) (4.7o):[24]



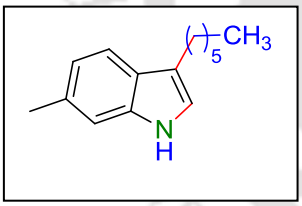
Brown solid; Yield: 89% (0.195 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (br s, 2H), 7.28-7.20 (m, 6H), 6.81 (dd, *J* = 8.7, 2.5 Hz, 2H), 6.79 (d, *J* = 2.4 Hz, 2H), 6.65 (d, *J* = 2.5 Hz, 2H), 5.73 (s, 1H), 3.67 (s, 6H), 1.29 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.7, 148.8, 140.9, 131.9, 128.4, 127.6, 125.2, 124.5, 119.6, 111.9, 111.8, 102.1, 55.9, 39.9, 34.5, 31.5.

3,6-Dimethyl-1H-indole (4.6bb):[40]



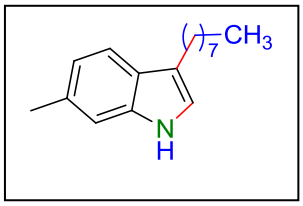
Light yellow oil; Yield: 80 % (0.102 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (br s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.17 (s, 1H), 6.99 (d, J=8.0 Hz, 2H), 2.49 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 136.8, 131.7, 126.3, 121.0, 121.0, 118.6, 111.7, 111.0, 21.8, 9.8.

6-Methyl-3-hexyl-1H-indole (4.6cc):[16e]



Pale red oil; Yield: 68 % (0.146 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (br s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.17 (s, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.91(br s, 1H) 2.75 (t, *J* = 7.7 Hz, 2H), 2.48 (s, 3H), 1.75-1.69 (m, 2H), 1.43-1.28 (m, 6H), 0.92 (t, *J* = 6.64 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 136.9, 131.7, 125.6, 120.9, 120.4, 118.8, 117.2, 111.1, 31.9, 30.3, 29.5, 25.4, 22.8, 21.8, 14.3.

6-Methyl-3-octyl-1H-indole (4.6dd):[12]



Light red oil; Yield: 63 % (0.153 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (br s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.14 (s, 1H), 6.94 (d, *J*=8.0 Hz, 1H), 6.89 (br s, 1H) 2.71 (t, *J* = 7.7 Hz, 2H), 2.45 (s, 3H), 1.70-1.54 (m, 2H), 1.39-1.35 (m, 2H), 1.33-1.23 (m, 8H), 0.87 (t, *J* =7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.9, 131.7, 125.6, 120.9, 120.4, 118.8, 117.2, 111.1, 32.1, 30.3, 29.8, 29.7, 29.5, 25.4, 22.8, 21.8, 14.3.

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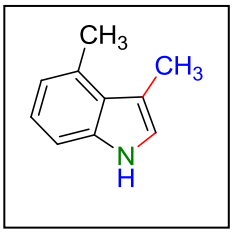
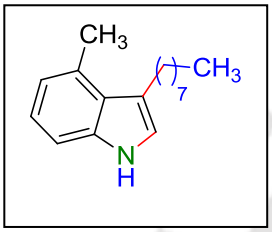
3,4-Dimethyl-1H-indole (4.6ee):[46]



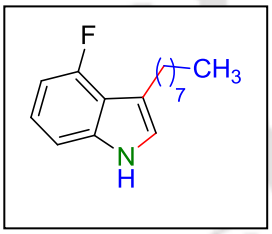
Light yellow oil; Yield: 74 % (0.107 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (br s, 1H), 7.20 (d, *J* = 8.1 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.94 (br s, 1H), 6.84 (d, *J*=7.0 Hz, 1H), 2.76 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.9, 131.4, 126.7, 122.1, 121.9, 120.7, 112.7, 109.1, 20.2, 13.2.

4-Methyl-3-octyl-1H-indole (4.6ff):



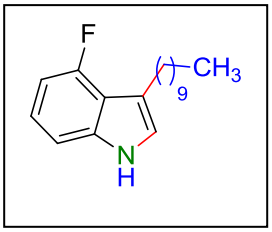
Light yellow oil; Yield: 63 % (0.153 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (br s, 1H), 7.21 (d, *J* = 8.1 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 2.3 Hz, 1H), 6.86 (d, *J* = 7.1 Hz, 1H), 2.93 (t, *J* = 7.6 Hz, 2H), 2.74 (s, 3H), 1.74-1.69 (m, 2H), 1.48-1.28 (m, 10H), 0.92 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.9, 131.7, 125.6, 120.9, 120.4, 118.8, 117.2, 111.1, 31.9, 30.3, 29.8, 29.4, 25.3, 22.84, 21.8, 14.3, 14.2. HRMS (EI): *m/z* calcd. for $C_{17}H_{24}NNa$: 265.1807 $[M+Na]^+$; found: 265.1817.

4-Fluoro-3-octyl-1H-indole (4.6gg):



Light yellow oil; Yield: 45 % (0.111 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (br s, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 7.11-7.06 (m, 1H), 6.93 (br s, 1H), 6.77-6.74 (m, 1H), 2.85 (t, *J* = 7.7 Hz, 2H), 1.74-1.69 (m, 2H), 1.43-1.26 (m, 10H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.6 (d, *J* = 246.8 Hz), 139.3 (d, *J* = 12.1 Hz), 122.4 (d, *J* = 7.9 Hz), 121.1, 116.4 (d, *J* = 20.0 Hz), 116.3 (d, *J* = 3.4 Hz), 107.1 (d, *J* = 3.5 Hz), 104.5 (d, *J* = 19.6 Hz), 32.1, 31.0, 29.6, 29.6, 29.5, 26.5, 22.8, 14.3. HRMS (EI): *m/z* calcd. for $C_{16}H_{22}FN$: 247.1716 $[M^+]$; found: 247.1711.

4-Fluoro-3-decyl-1H-indole (4.6hh):



Light yellow oil; Yield: 80 % (0.137 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (br s, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 7.10-7.06 (m, 1H), 6.92 (br s, 1H), 6.77-6.74 (m, 1H), 2.85 (t, *J* = 7.7 Hz, 2H), 1.74-1.69 (m, 2H), 1.43-1.29 (m, 14H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.6 (d, *J* = 246.6 Hz), 139.3 (d,

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J = 12.0 Hz), 122.4 (d, *J* = 8.0 Hz), 121.1, 116.4 (d, *J* = 20.4 Hz), 116.3 (d, *J* = 3.4 Hz), 107.2 (d, *J* = 3.5 Hz), 104.5 (d, *J* = 19.8 Hz), 32.1, 31.0, 29.8, 29.8, 29.7, 29.6, 29.5, 26.6, 22.8, 14.3. HRMS (ESI+): *m/z* calcd. for $C_{18}H_{27}FN$: 267.2128 $[M+H]^+$; found: 267.2129.

4.6. References:

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4.7. ^{1}H and ^{13}C NMR spectra:

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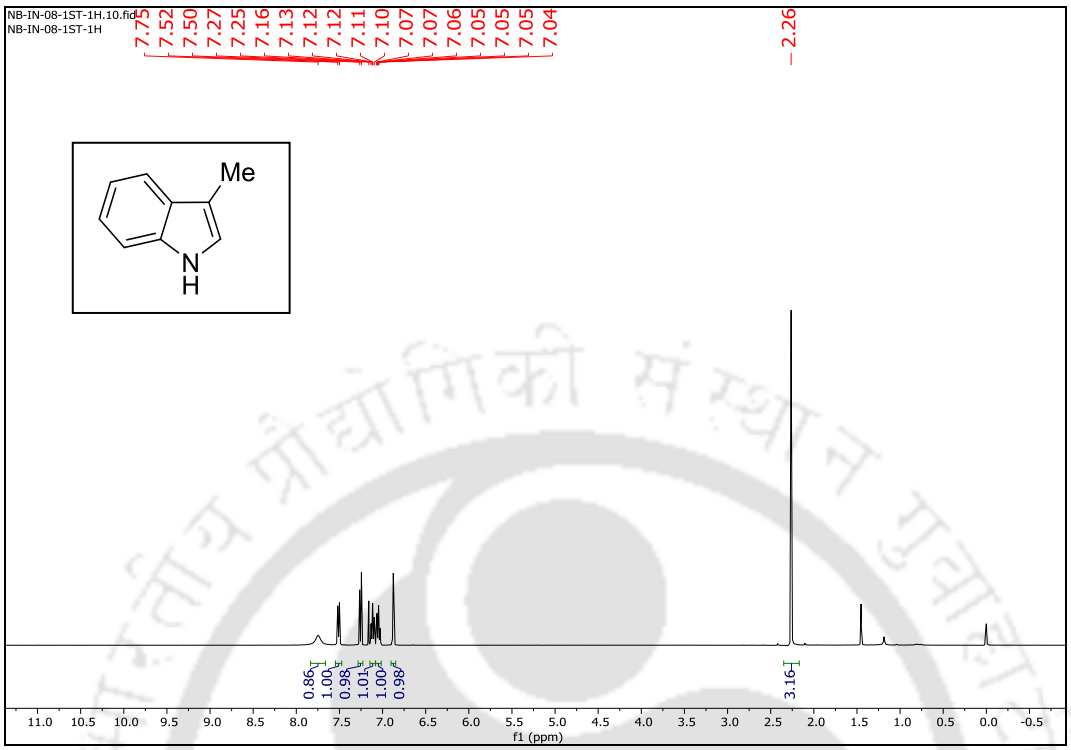

Figure 4.1: ^{1}H NMR spectra of **4.6a** in $CDCl_3$

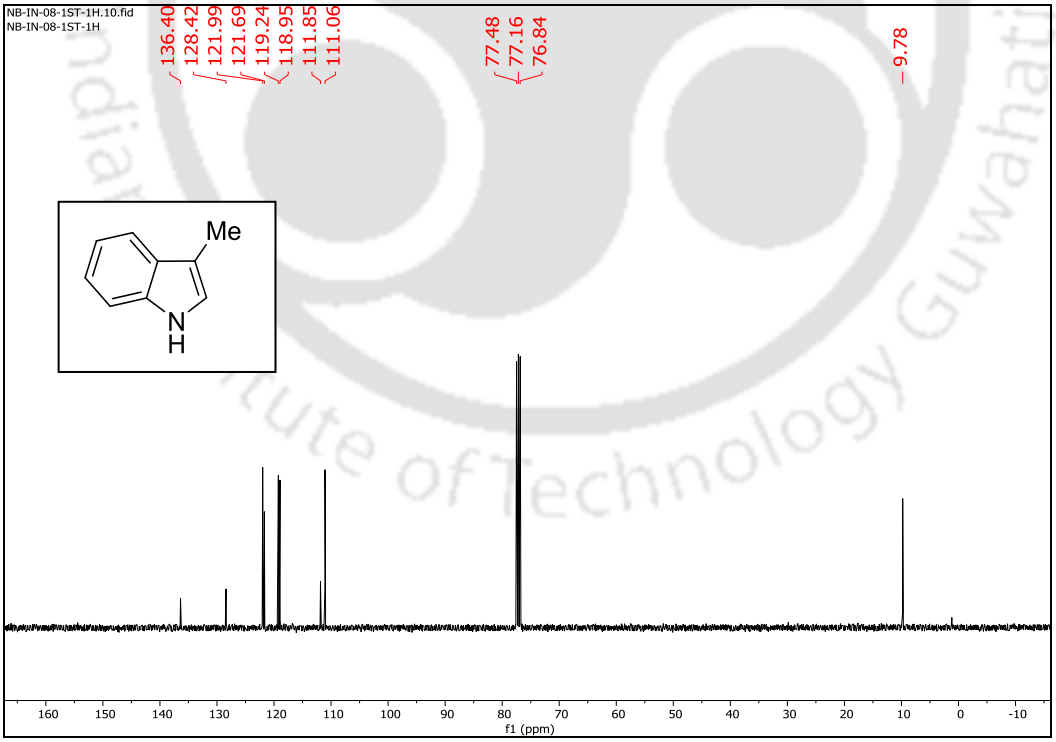

Figure 4.2: ^{13}C NMR spectra of **4.6a** in $CDCl_3$

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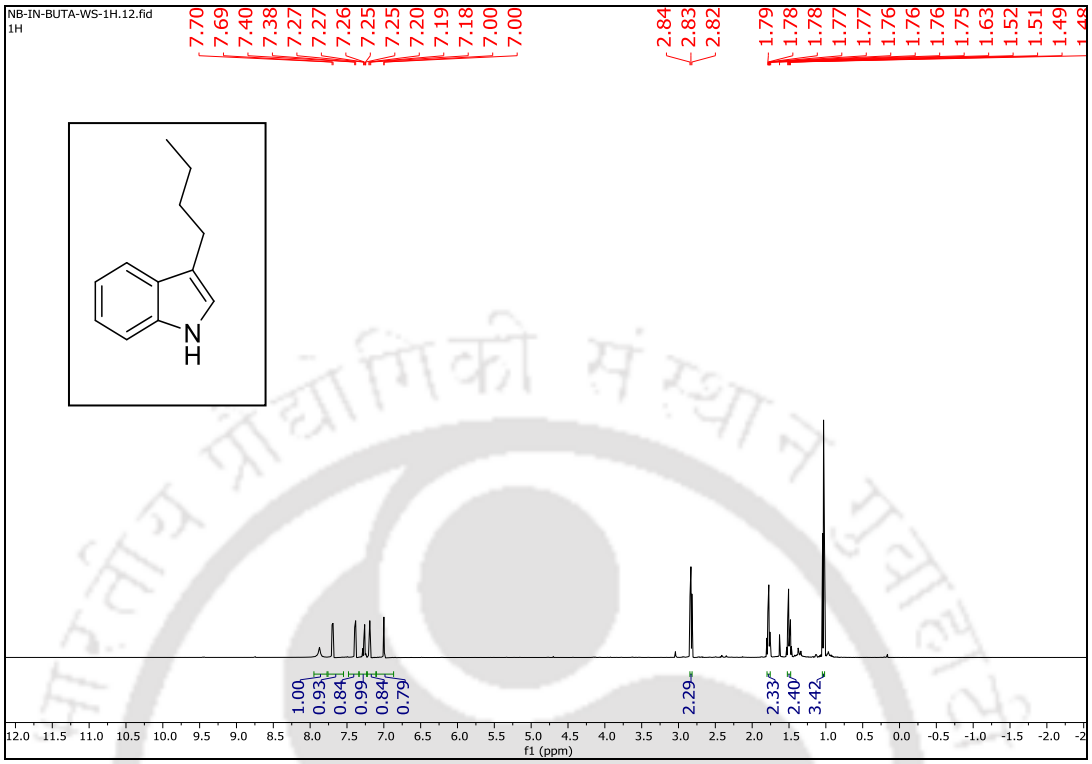

Figure 4.3: ^{1}H NMR spectra of **4.6c** in $CDCl_3$

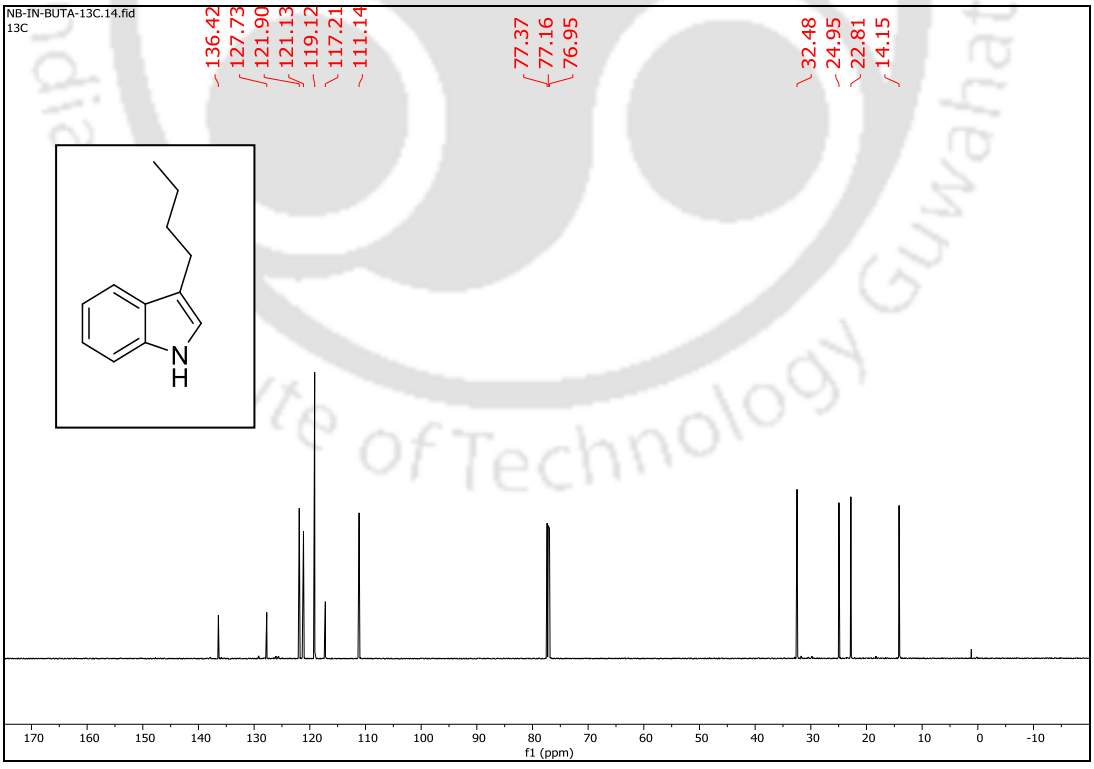

Figure 4.4: ^{13}C NMR spectra of **4.6c** in $CDCl_3$

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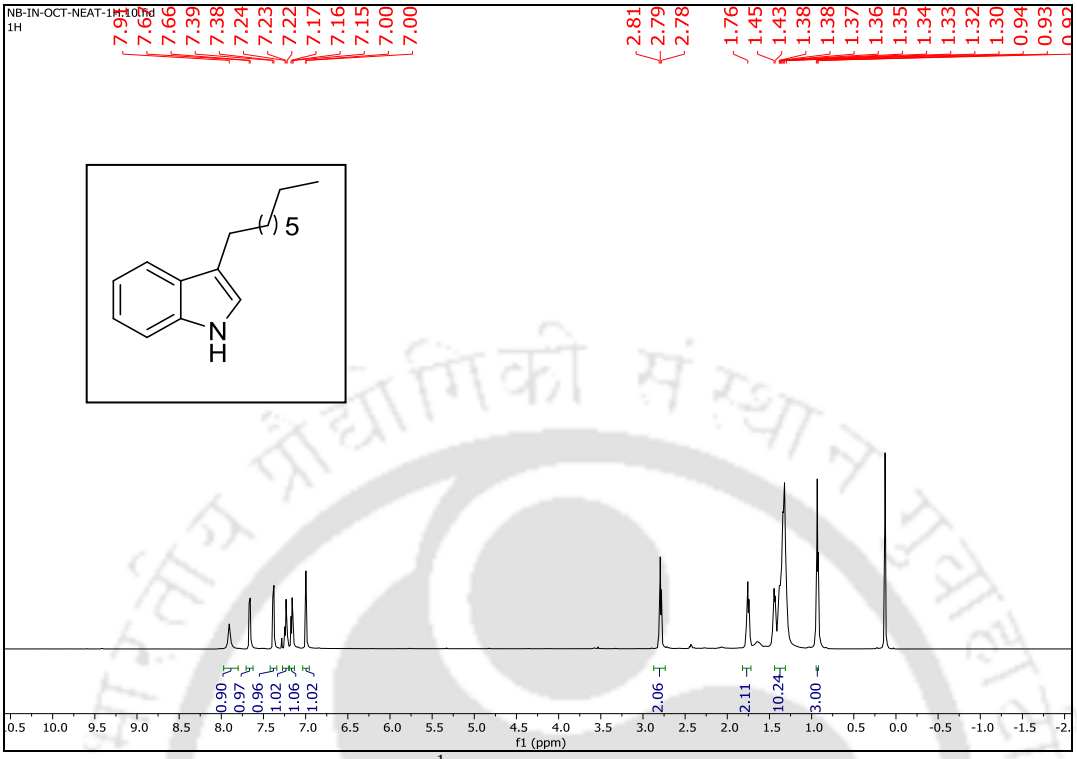

Figure 4.5: ^{1}H NMR spectra of **4.6e** $CDCl_3$

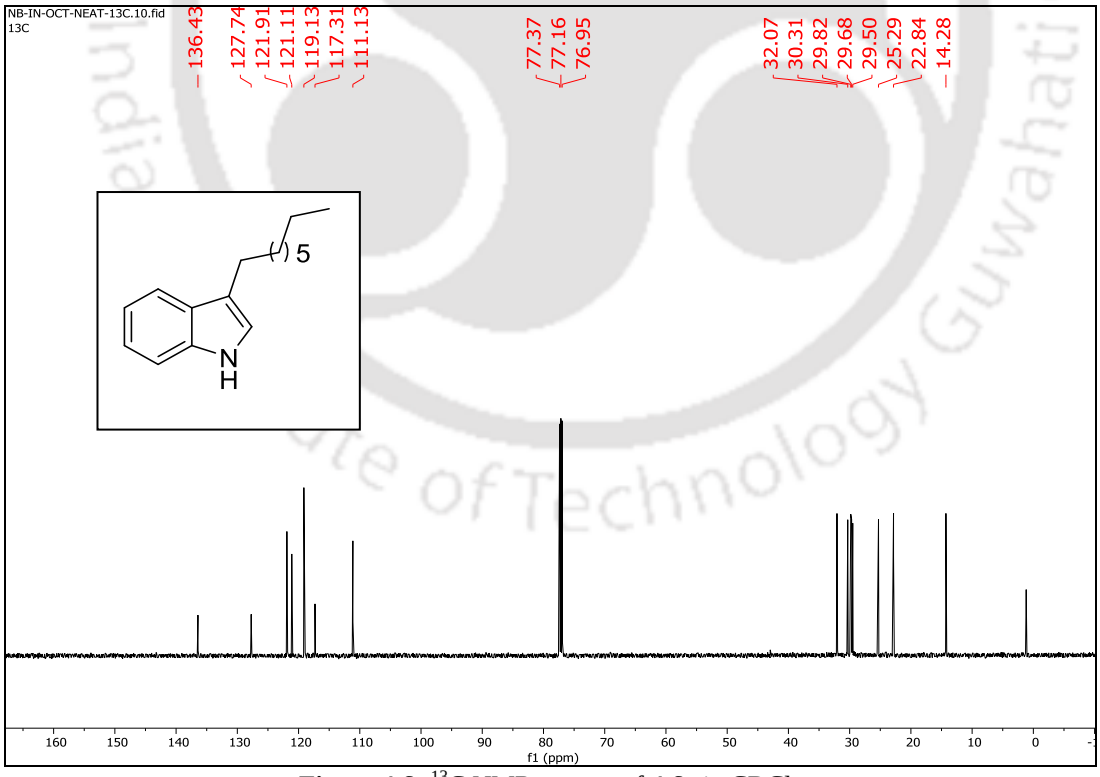

Figure 4.6: ^{13}C NMR spectra of **4.6e** in $CDCl_3$

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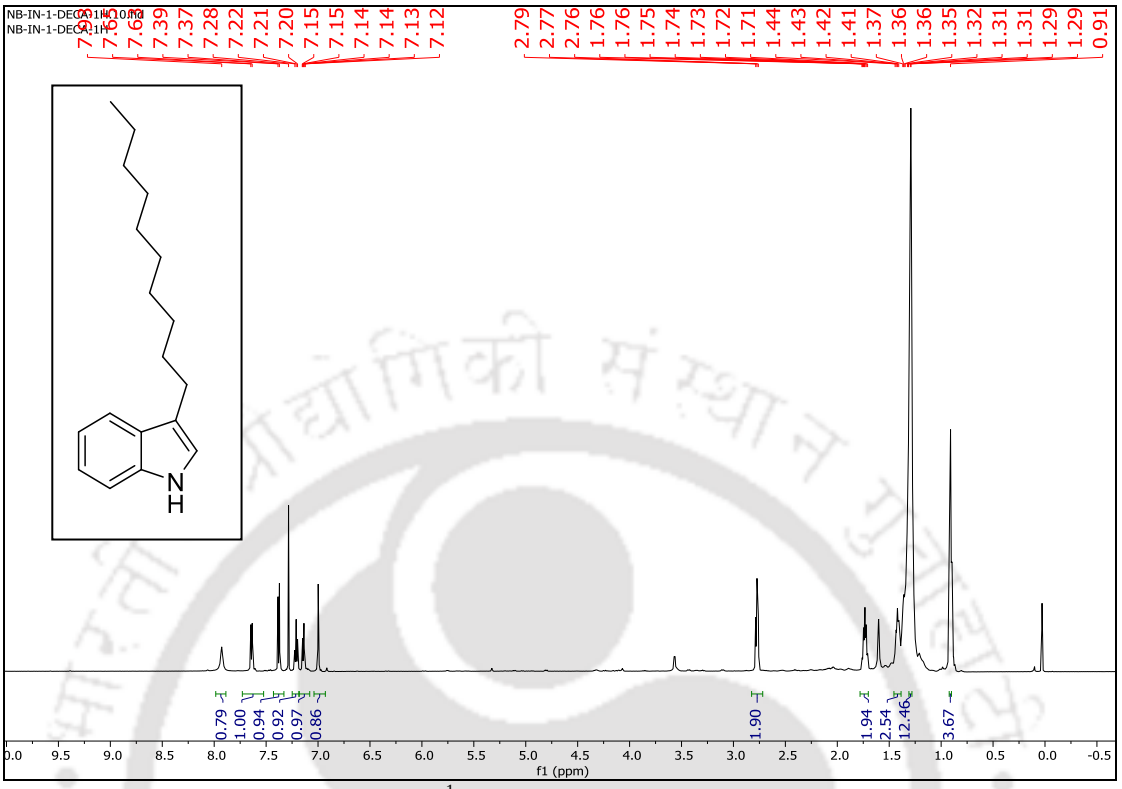

Figure 4.7: ^{1}H NMR spectra of **4.6f** in $CDCl_3$

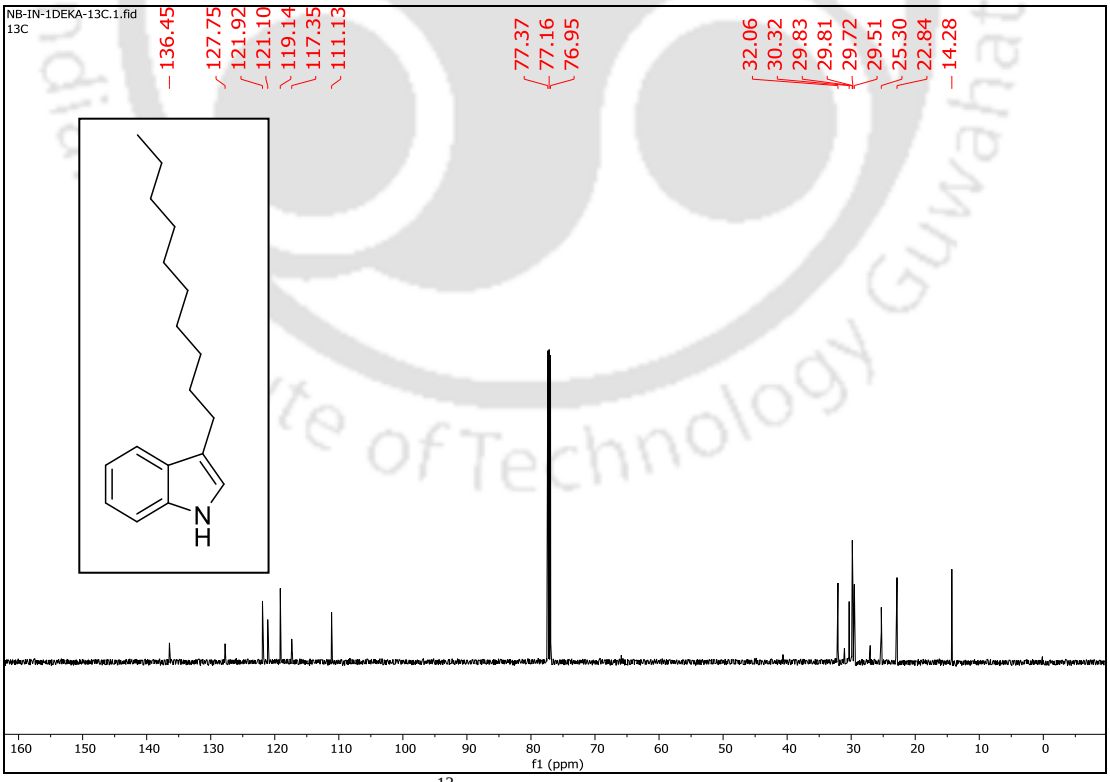

Figure 4.8: ^{13}C NMR spectra of **4.6f** in $CDCl_3$

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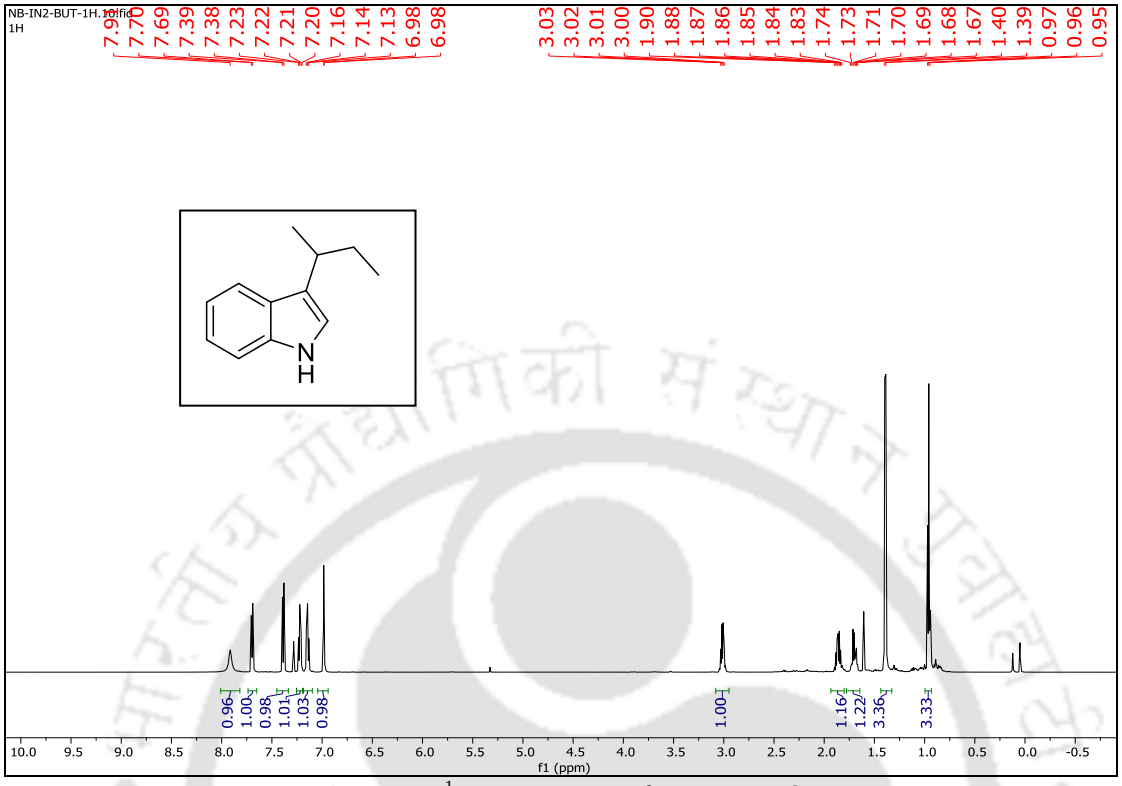

Figure 4.9: ^{1}H NMR spectra of **4.6g** in $CDCl_3$

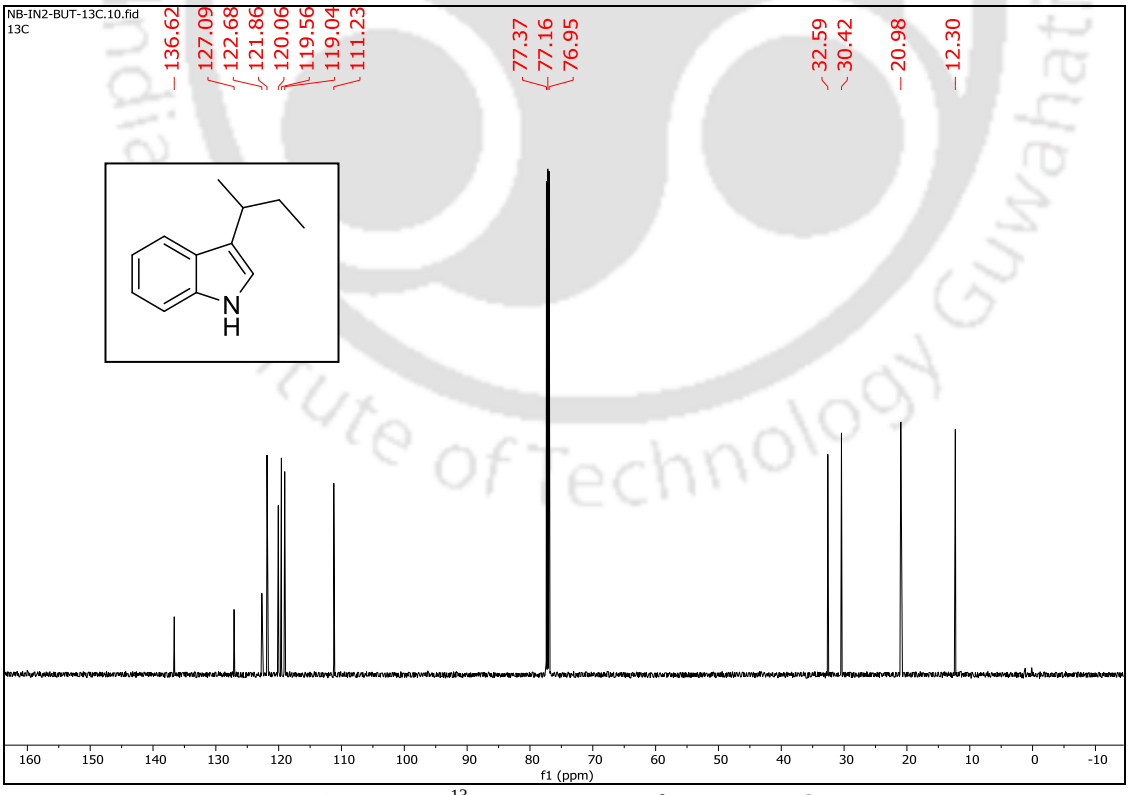

Figure 4.10: ^{13}C NMR spectra of **4.6g** in $CDCl_3$

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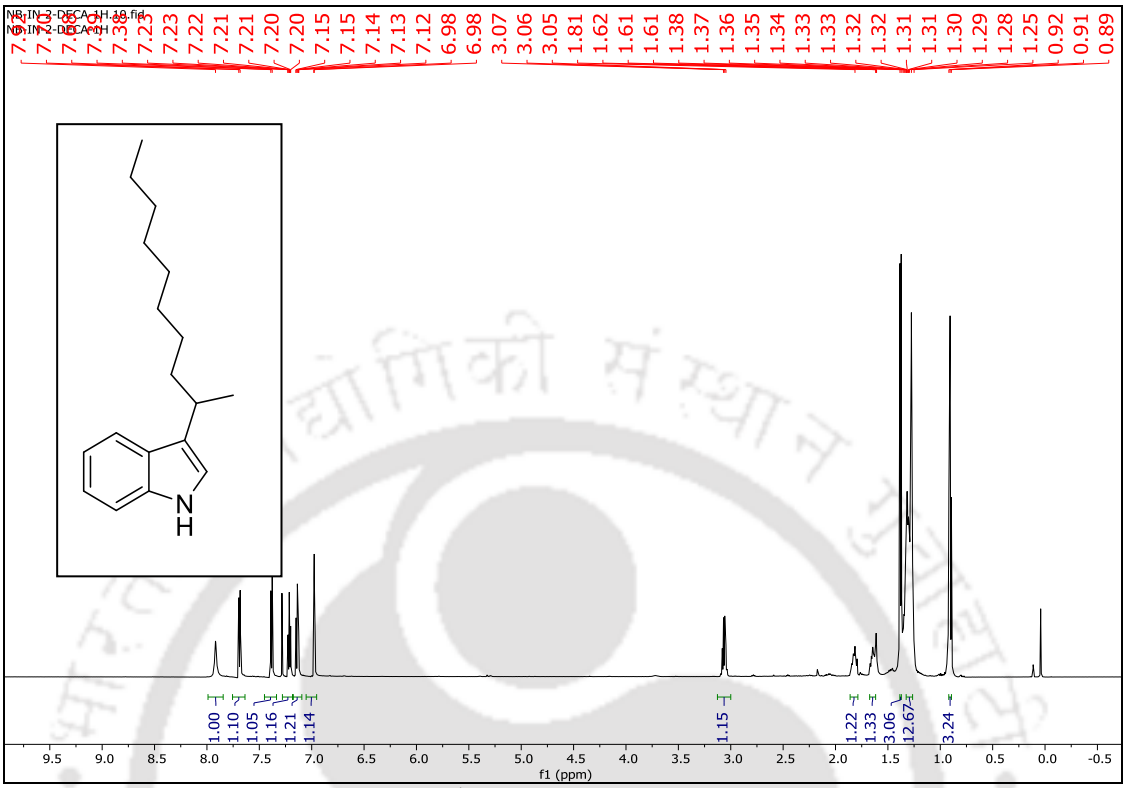

Figure 4.11: ^{1}H NMR spectra of **4.6i** in $CDCl_3$

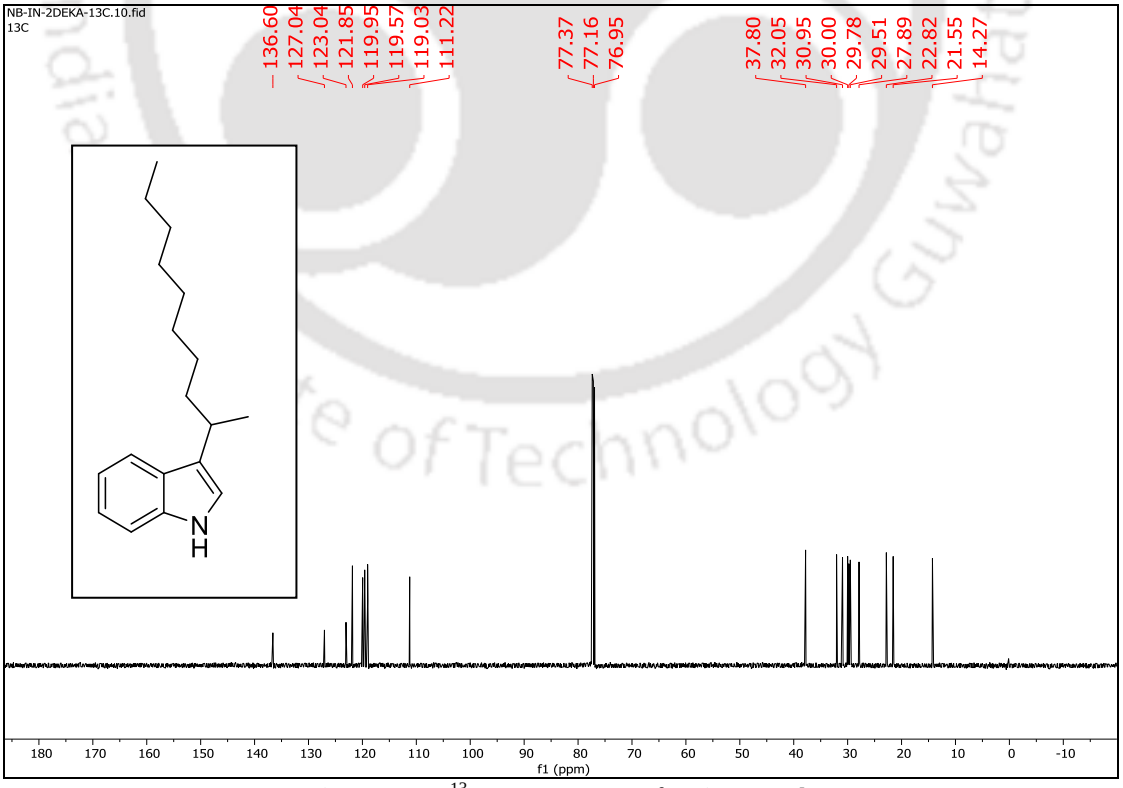

Figure 4.12: ^{13}C NMR spectra of **4.6i** in $CDCl_3$

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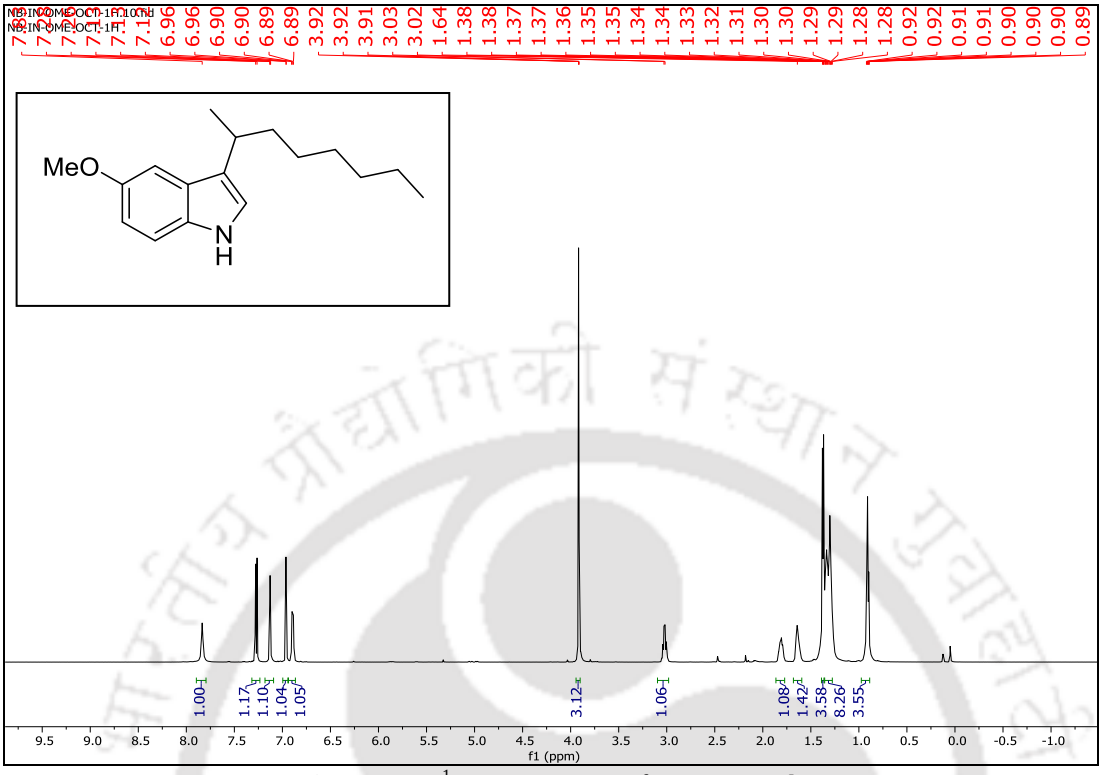

Figure 4.13: ^{1}H NMR spectra of **4.6z** in $CDCl_3$

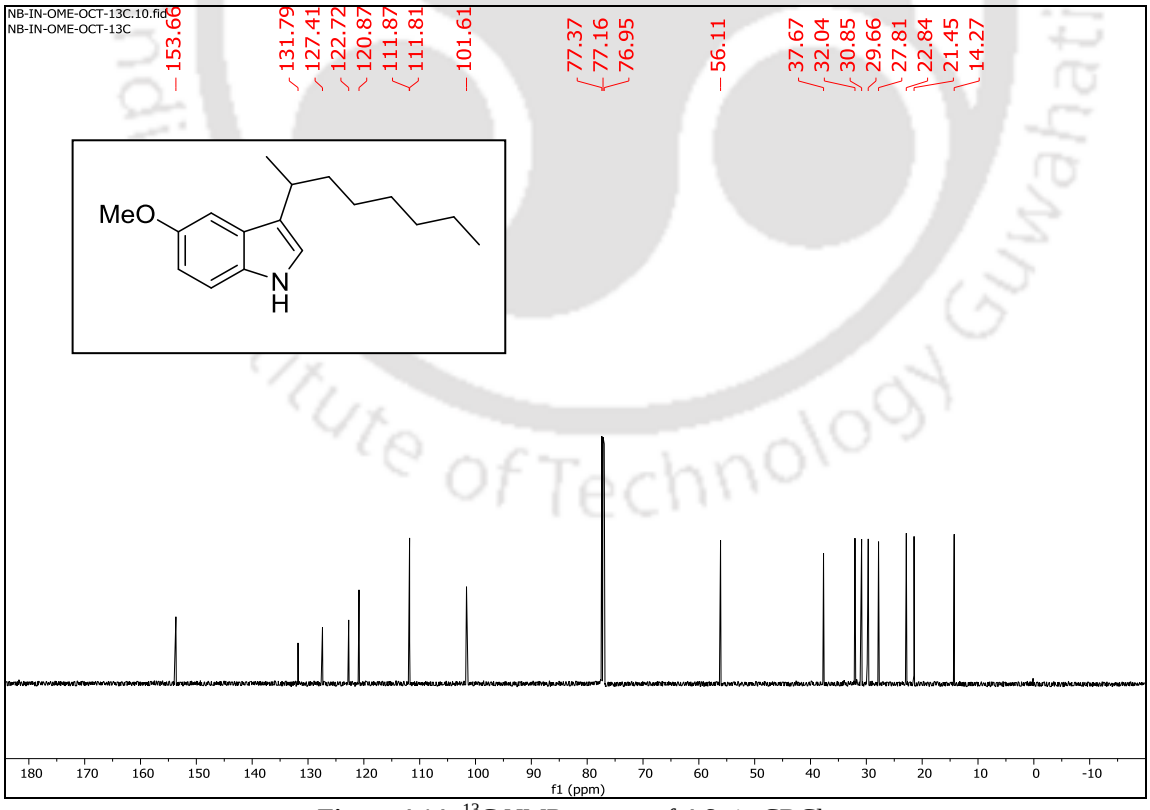

Figure 4.14: ^{13}C NMR spectra of **4.6z** in $CDCl_3$

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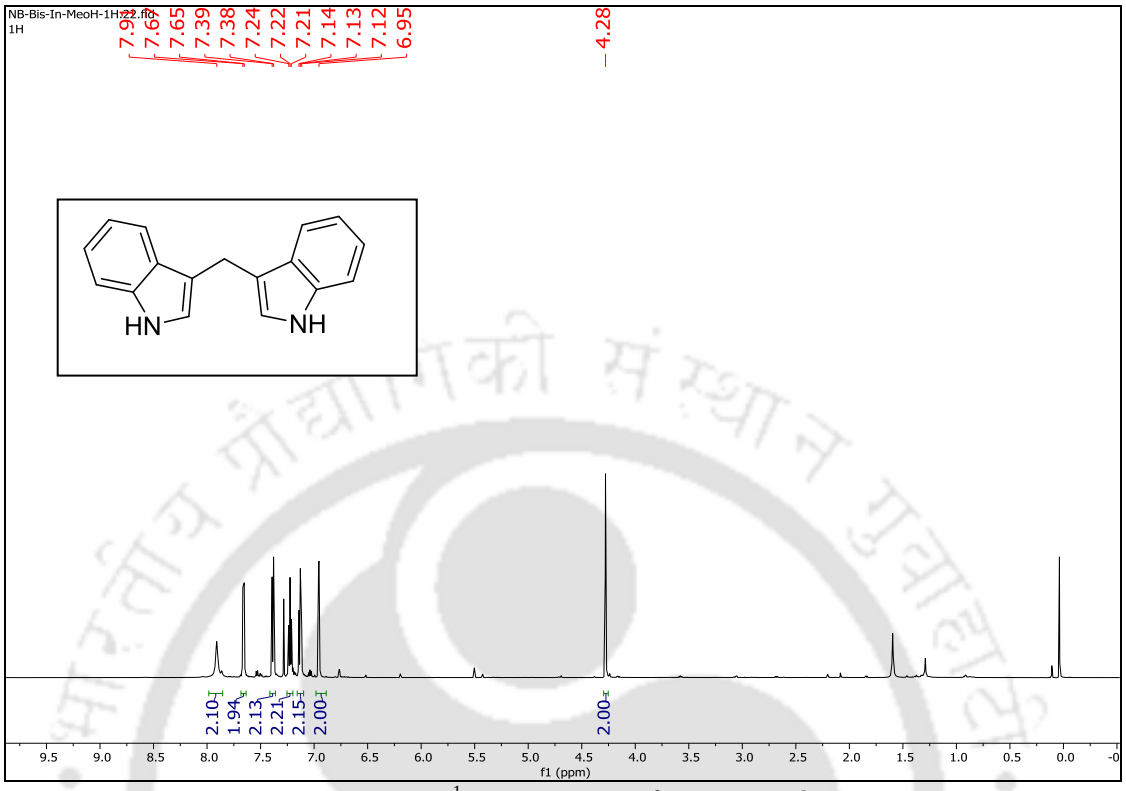

Figure 4.15: ^{1}H NMR spectra of **4.7a** in $CDCl_3$

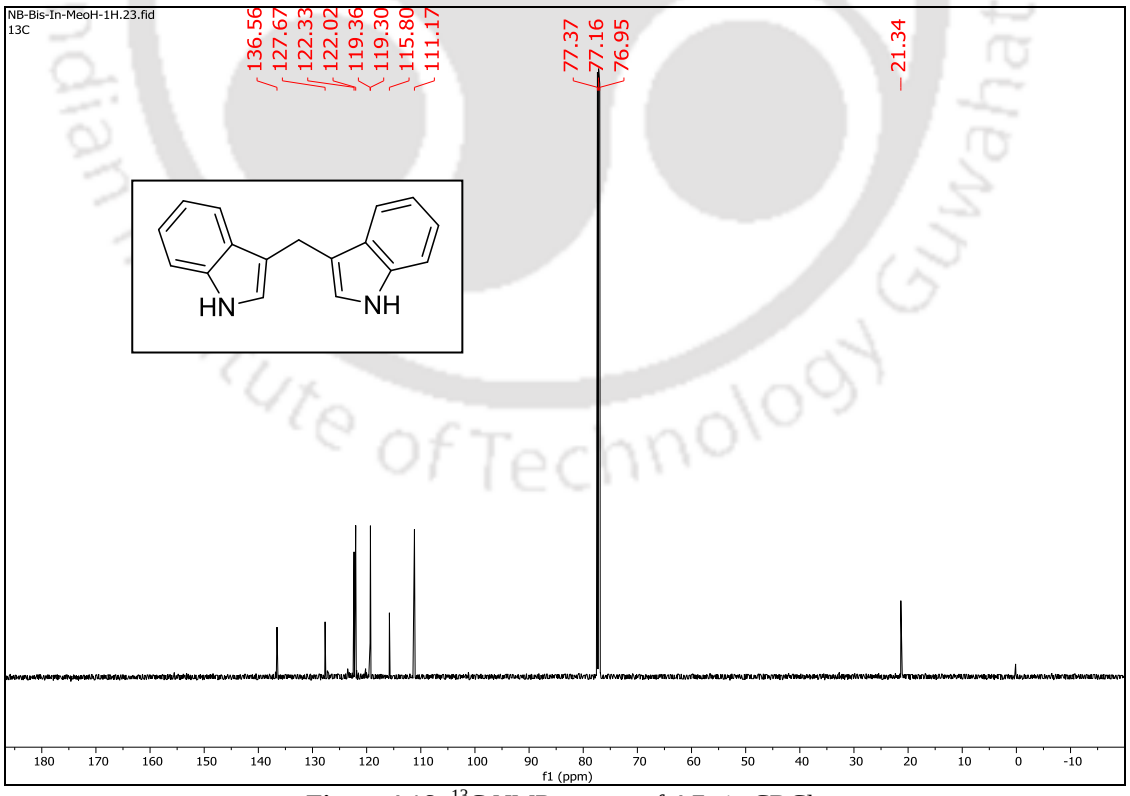

Figure 4.16: ^{13}C NMR spectra of **4.7a** in $CDCl_3$

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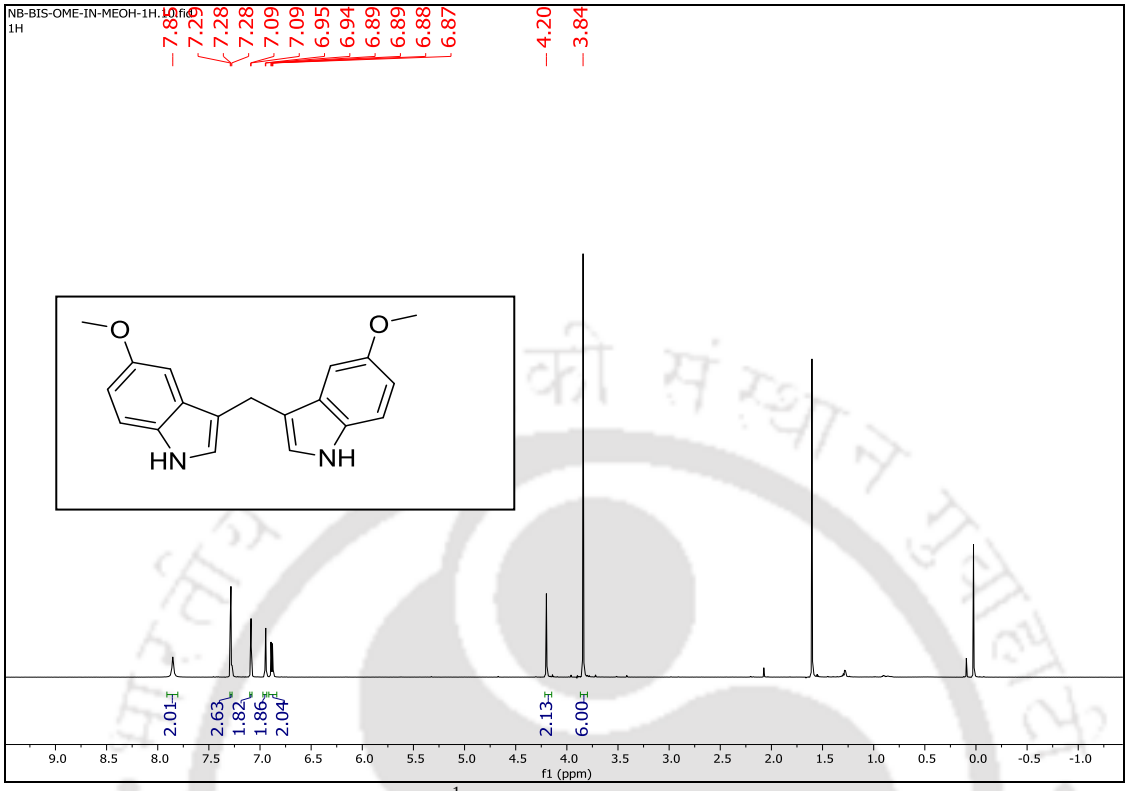

Figure 4.17: ^{1}H NMR spectra of **4.7f** in $CDCl_3$

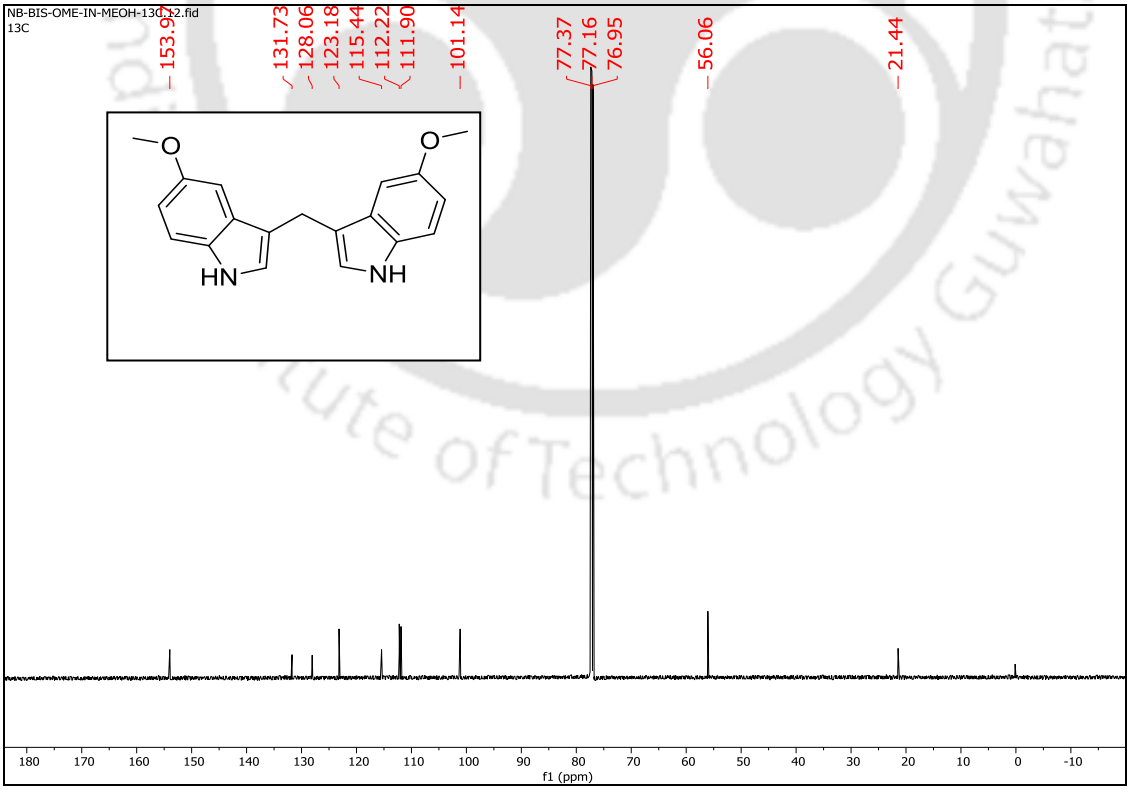

Figure 4.18: ^{13}C NMR spectra of **4.7f** in $CDCl_3$

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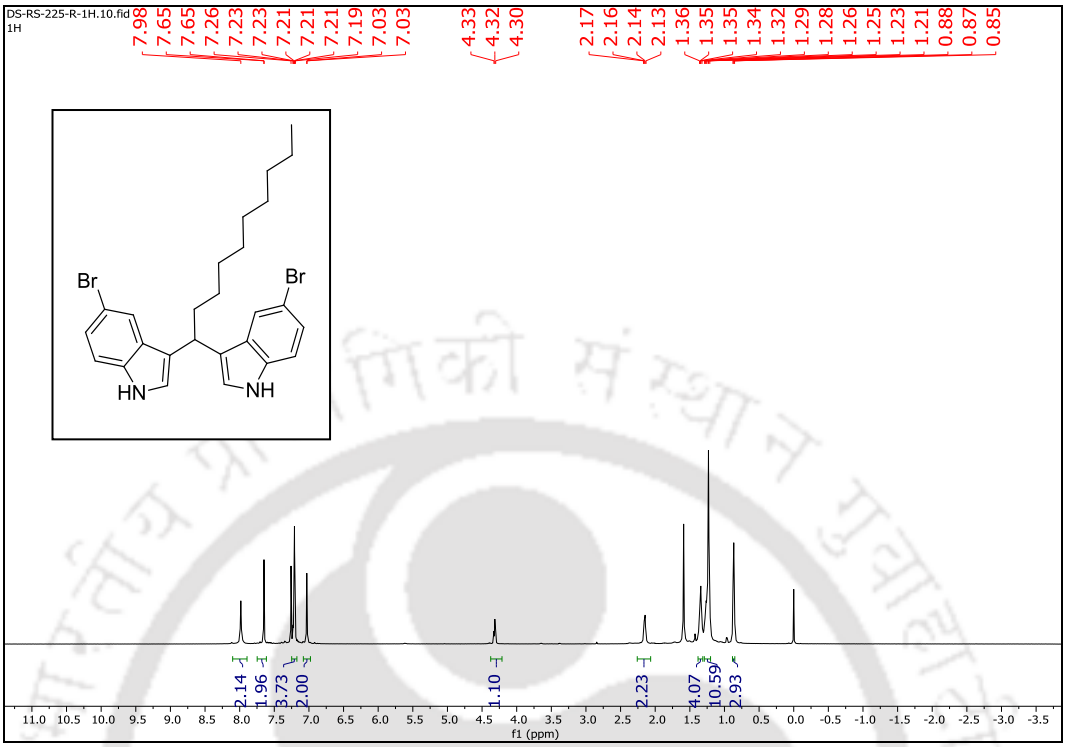

Figure 4.19: ^{1}H NMR spectra of **4.7k** in $CDCl_3$

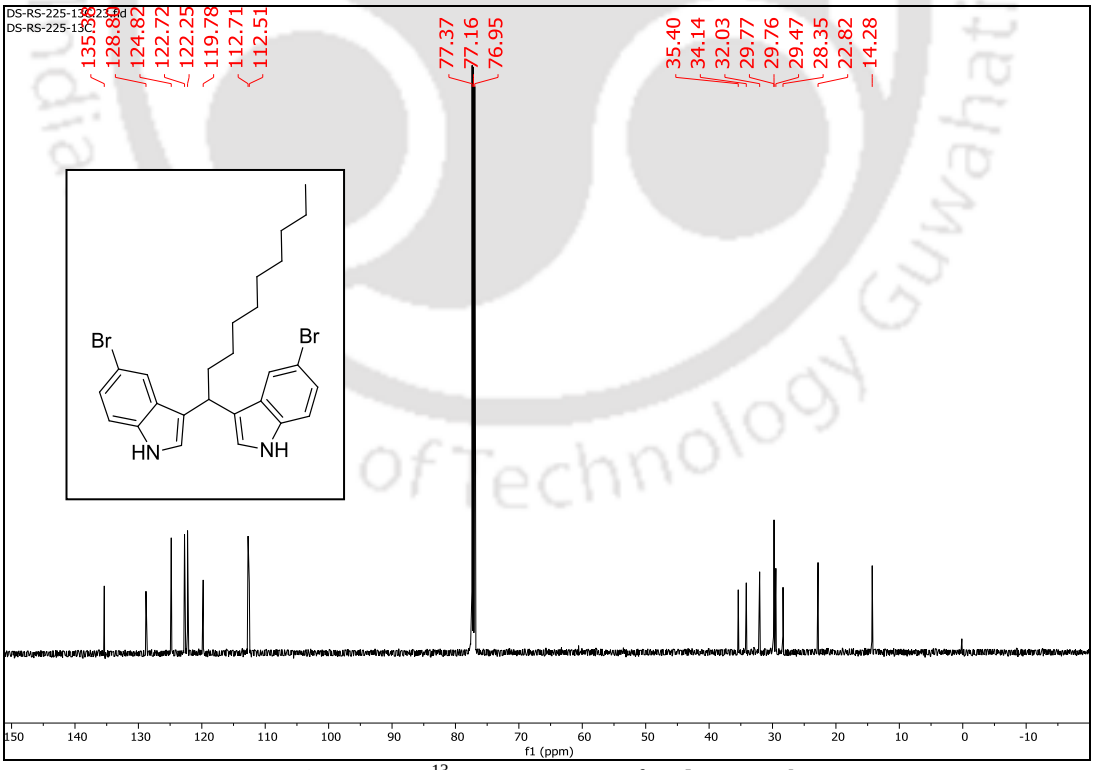

Figure 4.20: ^{13}C NMR spectra of **4.7k** in $CDCl_3$

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Chapter 5

Ru-Catalyzed Selective Catalytic Methylation and Methylenation Reaction Employing Methanol as the C1 Source

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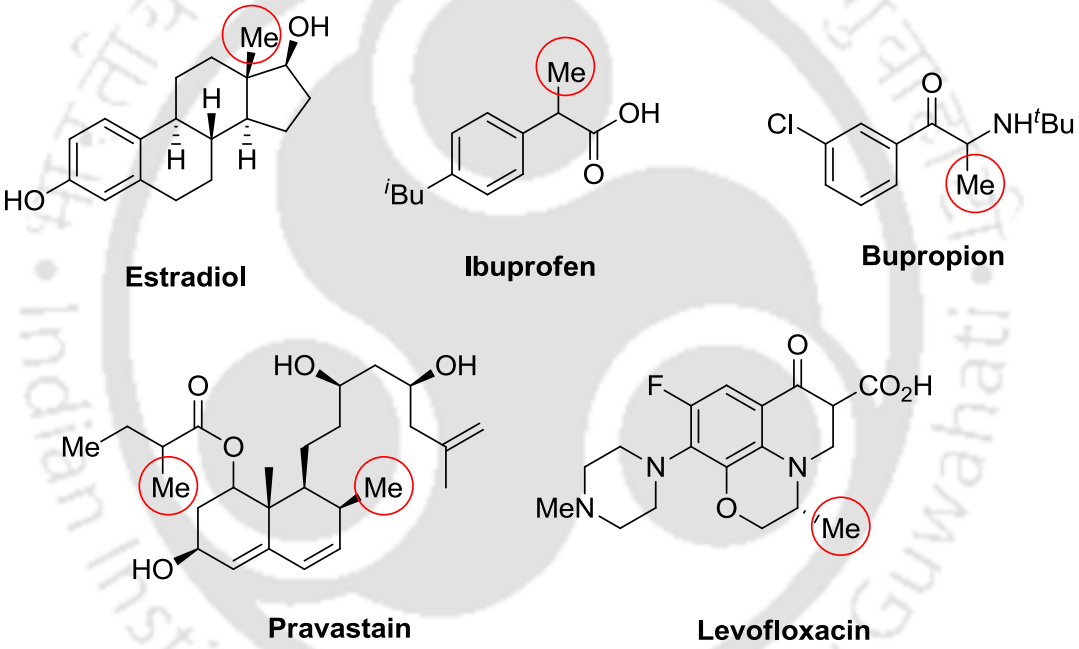
5.1. Introduction:

Methyl group is an important functionality found in many biologically active molecules[1] and plays a significant role in regulating pharmaceutical properties[2] of a molecule (Scheme **5.1**). A report says that around 67% of the top-selling drugs in 2011 contain at least one methyl group that is bound to a carbon, nitrogen, or oxygen atom.[3] In particular, the installation of methyl groups can dramatically improve IC_{50} values of a specific drug.[3,4] Therefore, the direct introduction of a methyl group to such moiety in a single step and in a greener way is an important area of scientific research.



Scheme 5.1: Biological important molecule bearing methyl group

Methanol can be renewably obtained from lignocellulosic biorefinery.[5] Thus, the applicability of methanol as a methylating agent relative to commonly employed methylating reagents such as diazomethane, dimethyl sulfate, and iodomethane[6] is highly desirable as methanol is considered as a sustainable and atom economical C1 source.[7] Recently, (de)hydrogenative[8] construction of C-C, C-N, and C-S bonds using renewable alcohols has attracted enormous attention due to its atom-efficient and environmentally benign nature. However, methylation reactions are quite challenging over alkylation[8c,9]

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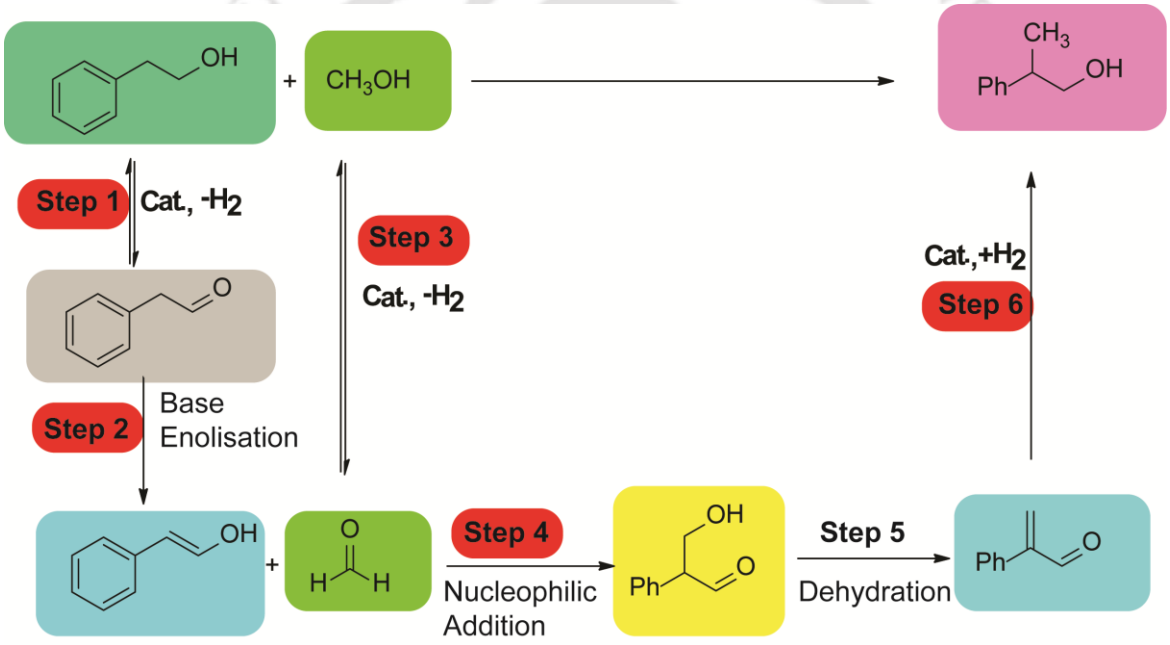
as large enthalpy (ΔH for methanol is +84 kJ mol^{-1})[10] is required to convert methanol to formaldehyde *via* dehydrogenation. Therefore, the development of new catalytic protocols for selective methylation is highly demanding.

The *β*-methylation of aliphatic alcohols plays an important role in the synthesis of higher or branched alcohols, in particular for alcohol biofuels.[10b,11] The coupling of methanol and primary alcohol[12] or secondary alcohol[12f,13] is highly challenging compare to the *α*-methylation of ketone[14] as it involves multiple reaction steps[12a] including dehydrogenation, aldol condensation and hydrogenation[12a] (Scheme **5.2**).



Scheme 5.2: Possible reaction mechanism

In 2014, *Beller and coworkers*[12a] first demonstrated *β*-methylation of 2-arylethanols. The cooperative reactivity of Ru-MACHO and Shvo's diruthenium complex is highly essential to afford the desired *β*-methylated product in good yield (Scheme **5.3**). With this dual catalyst system, a series of functionalized and substituted 2-arylethanol derivatives were methylated up to 87% yield.

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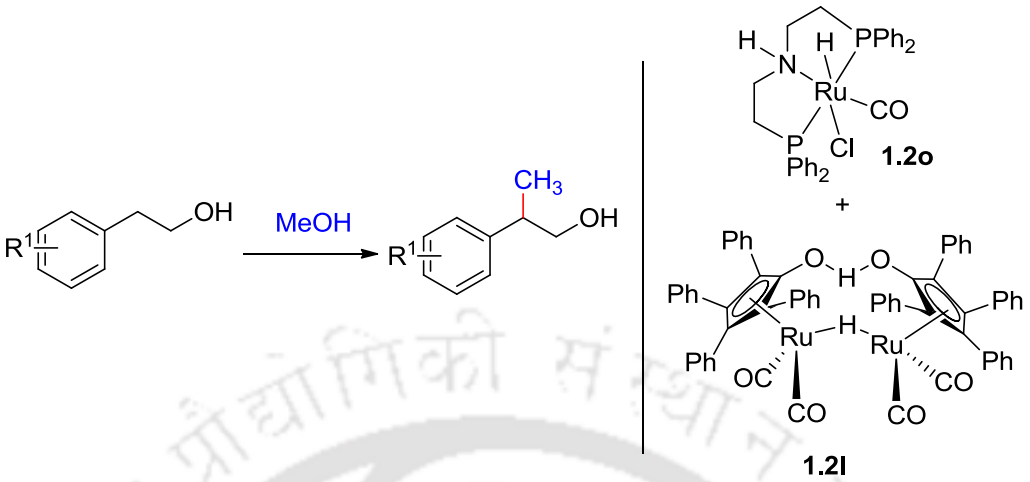
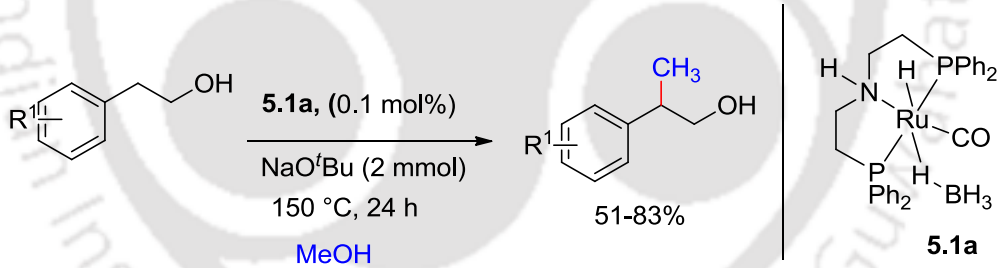


Scheme 5.3: *β*-Methylation of 2-arylethanols using Ru-MACHO and Shvo's diruthenium complex

In 2019, *Leitner and his group* demonstrated the selective *β*-methylation of 2-arylethanols in the presence of single Ru(II)-catalyst [$RuH(CO)(BH_4)(HN(C_2H_4PPh_2)_2)$]. Two equivalents of NaOMe are essential to promote the reaction at 150 °C[12b] (Scheme **5.4**).



Scheme 5.4: *β*-Methylation of 2-arylethanols using [$RuH(CO)(BH_4)(HN(C_2H_4PPh_2)_2)$] complex

Fe-catalyzed *β*-methylation of 2-arylethanols was recently reported by *Renaud*[12c] and *Morrill*,[12d] utilizing either a mixture of bases or applying of trimethylamine N-oxide additive and base (2 equiv.) (Scheme **5.5)**.

In 2020, *Leitner group* demonstrated Mn-catalyzed *β*-methylation of 2-arylethanols at higher temperature and high base loading.[12e] Heterogeneous catalysts such as iridium nanocluster[12f] and platinum on carbon[12g] are also utilized for this reaction.

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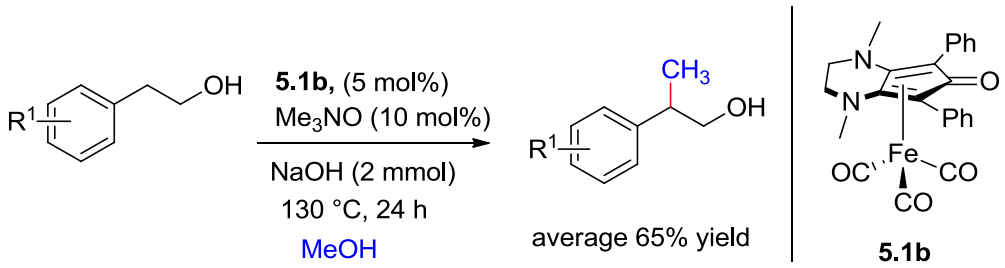
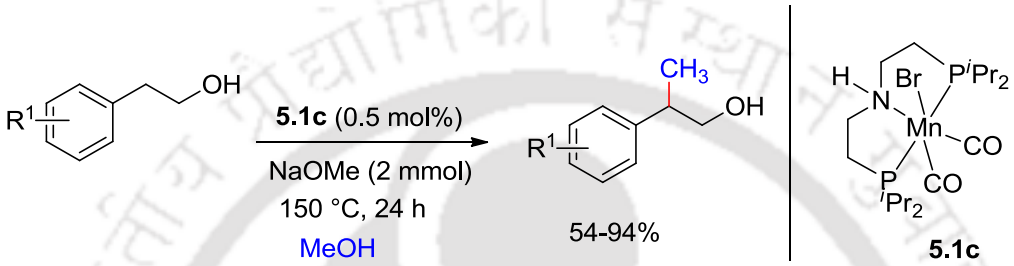
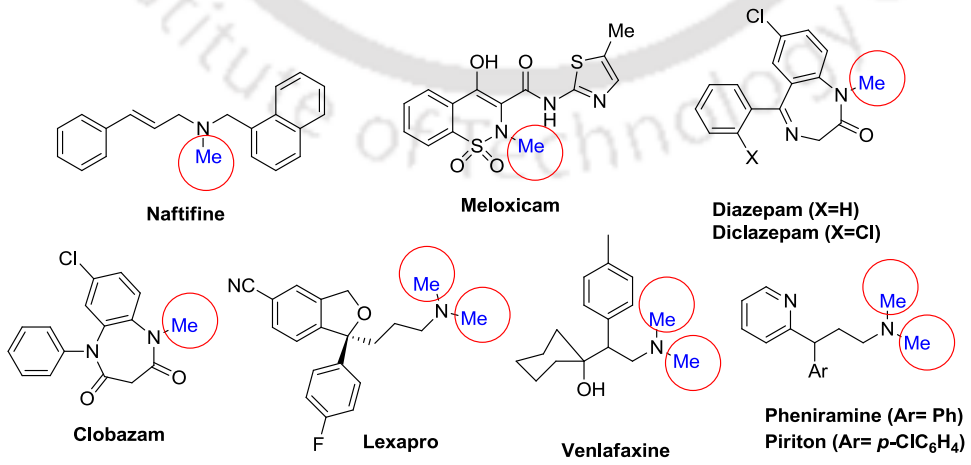


Scheme 5.5: *β*-Methylation of 2-arylethanols using Fe-complex



Scheme 5.6: *β*-Methylation of 2-arylethanols using Mn-complex

The direct *N*-methylation of amines is another crucial transformation in the synthesis of natural products, fine chemicals and pharmaceuticals (Scheme **5.7**).[15] Methyl halides as methylating agents have serious selectivity issues. Thus, it produces over alkylated products that reduces the overall yield of the desired product and make the separation of the products difficult.[16,17] Hence, the use of renewable MeOH as a methylating agent for selective mono or di-methylation of amines reaction is highly sustainable.



Scheme 5.7: Representative examples from pharmaceuticals containing *N*-methylamines

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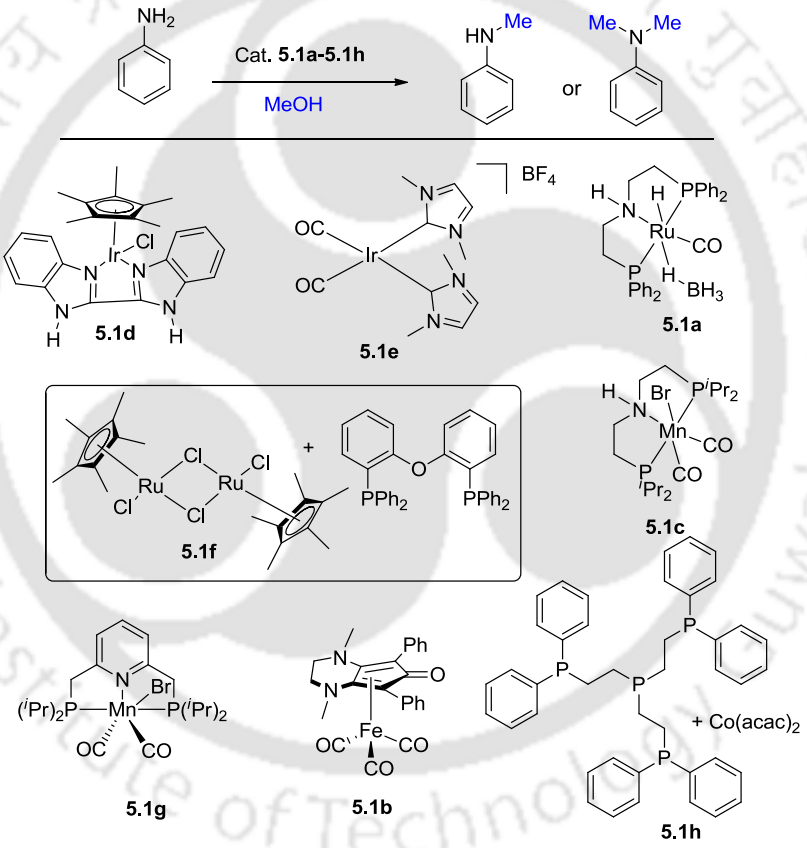
In the past, *N*-methylation of amines with methanol or with SCFs (super critical fluide) was mainly carried out using Lewis acid catalysts under harsh reaction conditions.[18a] Very recently transition metal catalyzed *N*-methylation of amines with methanol has been reported with homogeneous (Ir,[18b-f] Ru,[18g-h, 19a-c] Mn,[19d,] Fe[10a, 19e] and Co[19f]) (Scheme **5.8**), heterogeneous (Pd,[19g] Pt,[19h] and Al[19i]) and photocatalyst.[20]

Thus, the development of a robust catalyst, which can perform C-methylation and N-methylation reaction of various substrates, is highly desirable.



Scheme 5.8: *N*-Methylation of amines with methanol using homogeneous catalysts

5.2. Present work:

Engrossed by the salient benefit of methylation reaction using methanol herein the *β*-methylation of 2-phenyl alcohols has been demonstrated. Furthermore, the protocol was expanded toward selective mono *N*-methylation reaction of amine and dimerization

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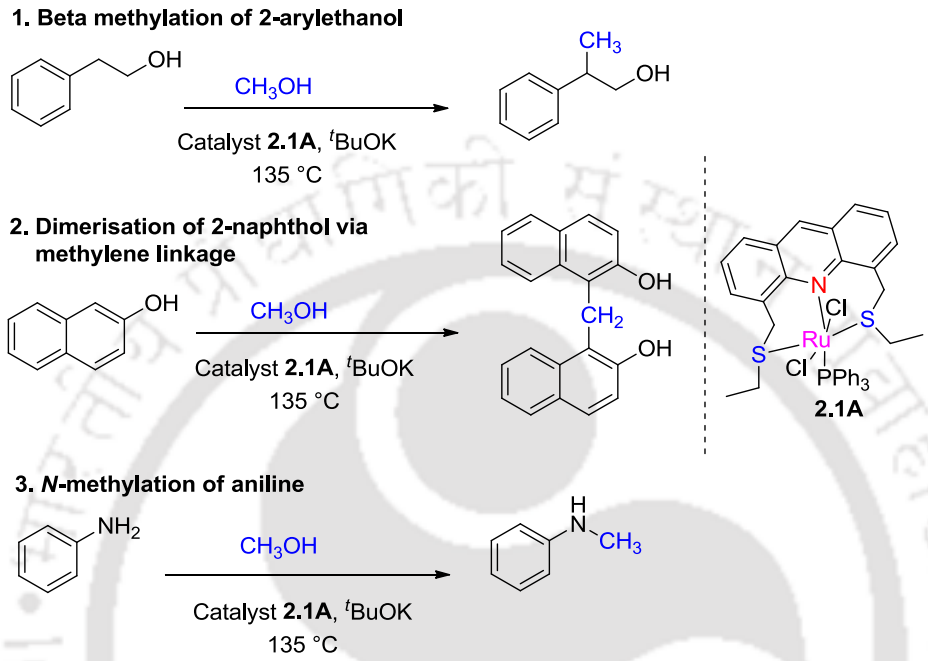
of 2-naphthol *via* methylene linkage to present the versatility of the developed catalyst[21,22] (Scheme **5.9**).



Scheme 5.9: C-methylation and *N*-methylation reactions using methanol as the methylating agent

5.2.1. Optimization of reaction conditions for the *β*-methylation of 2-phenylethanol:

In an initial experiment, the methylation of 2-phenylethanol (**5.4a**) was selected as a model system to find out the optimum reaction conditions. When 2-phenylethanol (1 mmol), MeOH (3 mL), KOH (1 mmol) was heated at 135 °C for 48 h in 100 mL Ace pressure tube in presence of 2 mol% catalyst **2.1A**, 68% 2-phenylpropan-1-ol (**5.5a**) was obtained (Table **5.1**, entry **1**). Interestingly, lower amount of MeOH (1 mL) under the similar condition, improved the yield of **5.5a** to 99%. However, lower reaction time (36 h) resulted in decrease of the yield of **5.5a** (Table **5.1**, entry **3**). On the other hand, within 36 h quantitative conversion was observed when ^{t}BuOK was used as base (Table **5.1**, entry **5**). Decreasing the amount of ^{t}BuOK (0.5 mmol) led to lower conversions of the

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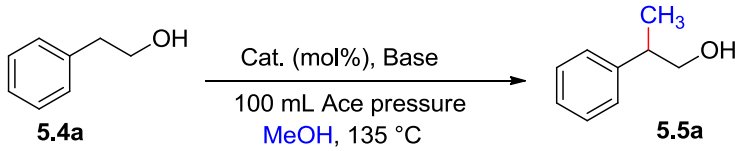
Table 5.1: Optimization of the reaction condition for the *β*-methylation of 2-phenylethanol.[a]



5.4a **5.5a**

Entry	Cat (mol %)	Base (mmol)	MeOH (mL)	Time (h)	Yield (%)[b]
1	**2.1A** (2 mol%)	KOH (1)	3	48	68
2	**2.1A** (2 mol%)	KOH (1)	1	48	98
3	**2.1A** (2 mol%)	KOH (1)	1	36	70
4	**2.1A** (2 mol%)	^{t}BuOK (1)	1	48	99
5	**2.1A** (2 mol%)	^{t}BuOK (1)	1	36	99
6	**2.1A** (2 mol%)	^{t}BuOK (1)	1	24	70
7	**2.1A** (2 mol%)	^{t}BuOK (0.5)	1	36	66
8	**2.1A** (2 mol%)	^{t}BuOK (0.5)	1	48	70
9	**2.1A** (2 mol%)	^{t}BuONa (1)	1	36	75
10	**2.1A** (2 mol%)	NaOH (1)	1	36	50
11	**2.1A** (2 mol%)	K_2CO_3 (1)	1	36	-
12	**2.1A** (1 mol%)	^{t}BuOK (1)	1	48	70
13	**2.1A** (2 mol%)	-	1	36	-
14	-	^{t}BuOK (1)	1	36	-
15[c]	**2.1A** (2 mol%)	^{t}BuOK (1)	1	48	75
16	**2.2A** (2 mol%)	^{t}BuOK (1)	1	36	-
17	**2.3A** (2 mol%)	^{t}BuOK (1)	1	36	-
18[d]	**2.1A** (2 mol%)	^{t}BuOK (1)	1	36	56

Reaction conditions[a]: alcohol (1 mmol), cat **2.1A** (2 mol%), base (1 mmol), MeOH (1 mL), 135 °C, 100 mL Ace pressure tube. [b]NMR yield using acetonitrile as standard. [c]110 °C. [d]30 mL Ace pressure tube.

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product even after 48 h. (Table **5.1**, entry **8**). Bases like ^{t}BuONa and NaOH gave moderate yield (Table **5.1**, entries **9**, **10**) under similar reaction conditions, whereas K_2CO_3 failed to give the desired product (Table **5.1**, entry **11**). Without the presence of any base, catalyst **2.1A** was failed to activate the alcohols; similarly, in absence of catalyst **2.1A**, 1 mmol ^{t}BuOK did not give any desired 2-phenylpropan-1-ol (**5.5a**) (Table **5.1**, entries **13**, **14**). Cat. **2.2A** and cat. **2.3A** are incompetent towards this β-C(sp^3)-methylation reaction (Table **5.1**, entry **16**, **17**). In 30 mL Ace pressure tube, the yield of the desire product is 56% (Table **5.1**, entry **18**).

5.2.2. Substrate scope for the β-methylation of 2-phenylethanol:

With optimized reaction conditions in hand (**Table 5.1**, entry **5**), the scope of the Ru-catalyzed β-C(sp^3)-methylation of alcohols was explored (Scheme **5.10**). Gratifyingly, high conversions and good yields were observed for substituted 2-arylethanols (Scheme **5.10**, **5.5a**-**5.5m**). Electron-donating substituents such as 2-(*p*-tolyl)ethanol (**5.4b**) and 2-(4-methoxyphenyl)ethanol (**5.4c**) afforded excellent yield of the corresponding methylated products (87% **5.5b** and 81% **5.5c**). 2-(2,4,6-Trimethoxyphenyl)propan-1-ol was afforded 92% yield (**5.5d**), indicating that the increased steric effect provided by aryl substitution at the 2- and 6-positions does not hinder β-C(sp^3)-methylation. Fluoro- and Chloro-substituted compounds were well tolerated. However, 2-(4-bromophenyl)ethanol gave the corresponding product in moderate yield 60% (**5.5g**) along with 20% (**5.5a**) dehalogenated product. Heterocyclic alcohol such as thiophene-substituted ethanol was smoothly converted to corresponding methylated product (**5.5h**) with high yield, 90%. The extended aromatic system, 2-napthylethanol was responded well under the reaction conditions. Unfortunately, 2-phenoxyethan-1-ol (**5.4k**) failed to give any product. When, 2-(4-aminophenyl)ethanol was used as substrate, both β-C(sp^3)-methylation and *N*-methylation occurred, providing **5.5l** in **60**% isolated yield together with some *N*-methylated product (**5.5m**), indicating that *N*-methylation is much faster than β-C(sp^3)-methylation reaction. 2-Phenylethanol having -CN or -NO_2 group in the aromatic nucleus failed to give the desired product.

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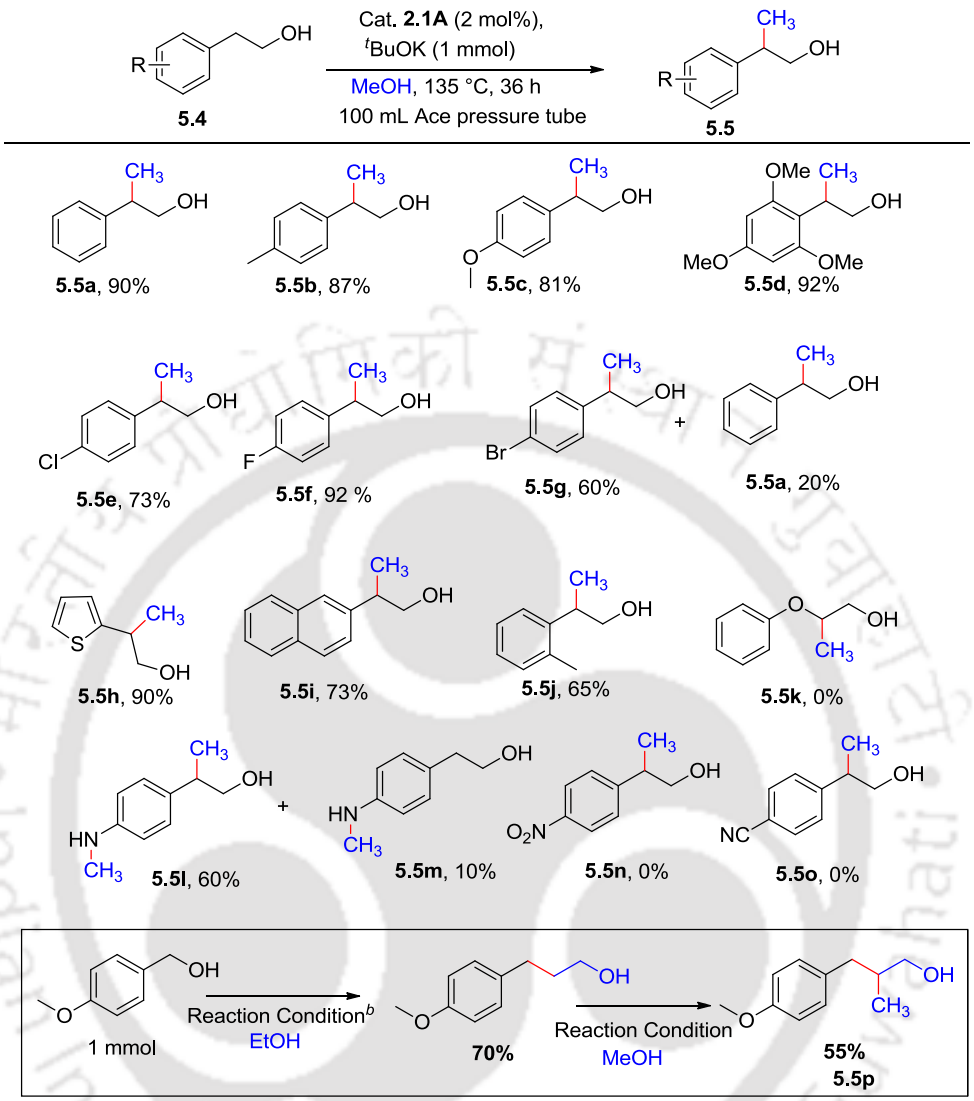
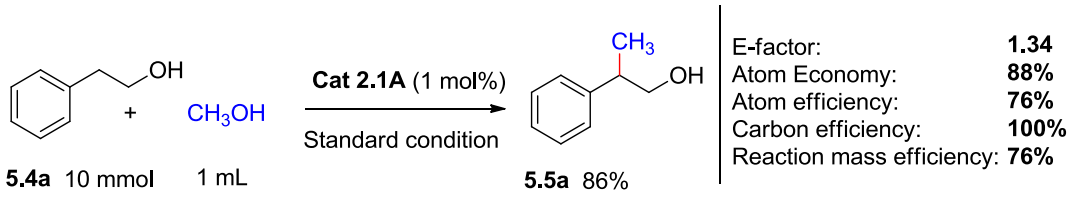


Scheme 5.10: Substrate scope for *β*-methylation of 2-phenylethanols.[a] [a] Reaction conditions: alcohol (1 mmol), cat **2.1A** (2 mol%), ^{t}BuOK (1 mmol), MeOH (1 mL), 135 °C, 100 mL Ace pressure tube. [b] Reaction conditions: alcohol (2 mmol), cat **2.1A** (1 mol%), ^{t}BuOK (1 mmol), EtOH (1 mL), 135 °C, 100 mL Ace pressure tube.



Scheme 5.11: Green chemistry metrics

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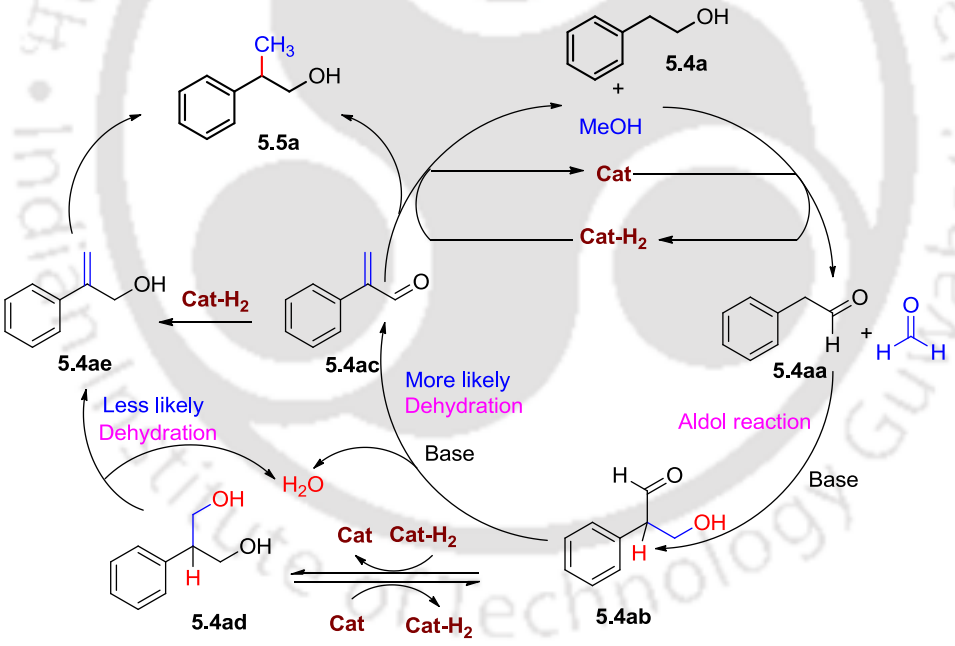
Methylation of 3-(4-methoxyphenyl)propan-1-ol (Scheme **5.10**) afforded **5.5p** in 55% isolated yield. It is important to note that the starting material 3-(4-methoxyphenyl)propan-1-ol was also prepared by reacting 4-methoxybenzyl alcohol with ethanol *via* BH reaction[23] employing the developed catalyst.

For the preparative scale synthesis of **5.5a**, it was possible to lower the catalyst loading (1 mol%) as well as **5.4a**:MeOH ratio.100% conversion of **5.4a** with high isolated yield (87%) of **5.5a** was obtained. The green chemistry metrics[24] of this reaction with an E-factor of 1.34, 88% atom economy, 76% atom efficiency, 100% carbon efficiency, and 76% reaction mass efficiency clearly exposed the technical and environmental benefits of this methodology (Scheme **5.11**).

5.2.3. Mechanistic and kinetic investigation:



Scheme 5.12: Proposed reaction mechanism

β-C(sp^3)-methylation method may likely follow a borrowing-hydrogen mechanism[12a,12g] (Scheme **5.12**). First, dehydrogenation of 2-phenylethanol and methanol leads to the formation of **5.4aa** and formaldehyde, which can form condensation product

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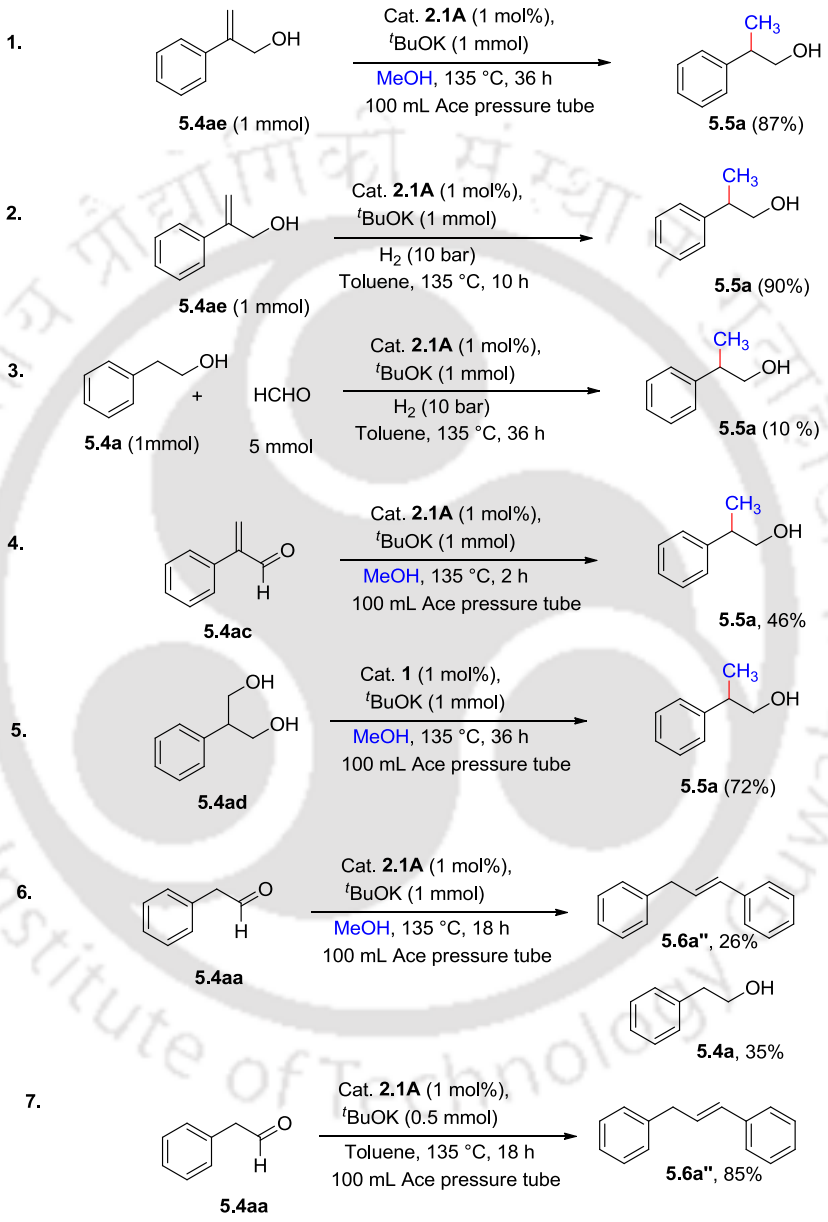
5.4ab. Compound **5.4ab** will eventually transform to **5.4ae** either *via* dehydration followed by hydrogenation of **5.4ac** or first hydrogenation followed by dehydration of **5.4ad**. Next, **5.4ae** will lead to the formation of **5.5a** *via* hydrogen-autotransfer process.



Scheme 5.13: Controlled experiments

To shed light on the proposed mechanism some control experiments (Scheme **5.13**) have been carried out. When preformed 2-phenylprop-2-en-1-ol **5.4ae** was subjected to the "standard" reaction conditions, β-C(sp^3)-methylated product **5.5a** was

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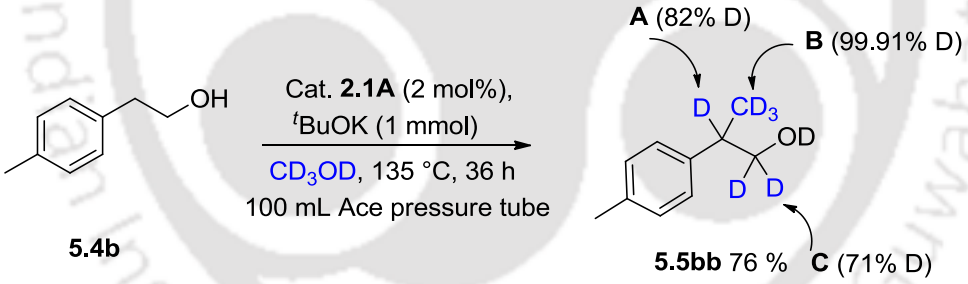
formed in 87% yield. The compound **5.4ae** was also converted to the **5.5a** (90%) in the presence of cat **2.1A** and molecular H_2. This clearly indicates the involvement of compound **5.4ae** as an intermediate in the β-C(sp^3)-methylation reaction. Intermediate **5.4ad** under the standard reaction conditions smoothly converted to **5.5a** (72%), which underpins **5.4ad** and might be another possible intermediate. The reaction with 2-phenylethanol **5.4a** and formaldehyde in hydrogen atmosphere (10 bar) in toluene keeping other conditions unaltered gives β-C(sp^3)-methylated product **5.5a** with 10% yield, supporting that formaldehyde is another plausible intermediate. The low yield of this experiment was possibly because of the low solubility of formaldehyde in toluene[12e] and the hydrogenation reaction of formaldehyde in the presence of a hydrogen atmosphere. When the intermediate **5.4ac** was subjected to the standard reaction conditions, **5.5a** was formed with 46% yield after 2 h. Under standard reaction conditions, phenylacetaldehyde (**5.4aa**) gave deoxygenative coupling[25] product (**5.6a″**) with 26% yield and 2-phenylethanol **5.4a** (35%). Thus, slow generation of phenylacetaldehye from **5.4a** is important to form the desired product **5.5a** in high yield.



Scheme 5.14. Labelling experiments with deuterated methanol

To gain further mechanistic insight, deuterium-labeling experiment with CD_3OD was carried out (Scheme **5.14**). The β-CD_3 group incorporation within alcohol yielded 76% β-CD_3-labeled 2-phenylethanol with 99.91% deuterium incorporation, in addition to significant deuterium incorporation at the α-(71% D) and β-(82% D) positions. This experiment confirmed methanol acting as the methylating agent and provided the support for the borrowing hydrogen mechanism.

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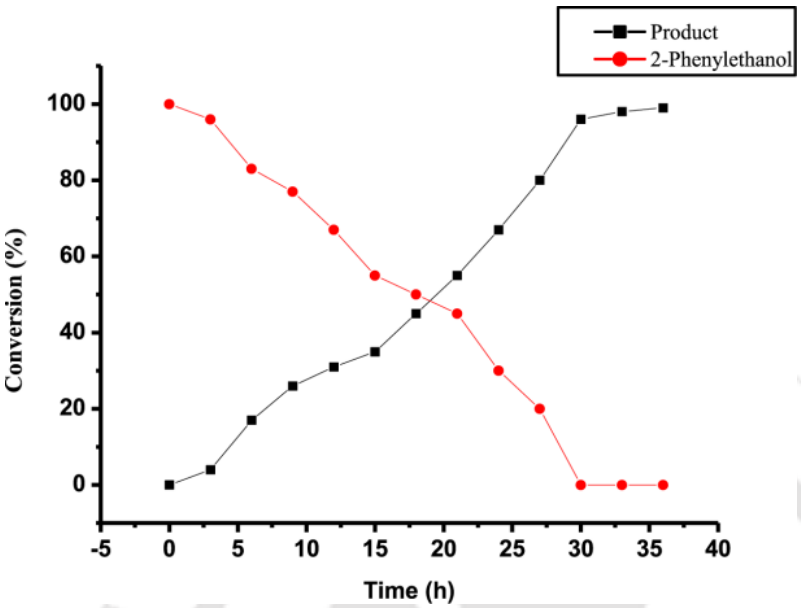

Figure 5.1: Time-dependent product distribution in *β*-methylation of 2-phenylethanol with methanol at 135 °C catalyzed by complex **2.1A**. (NMR yield)

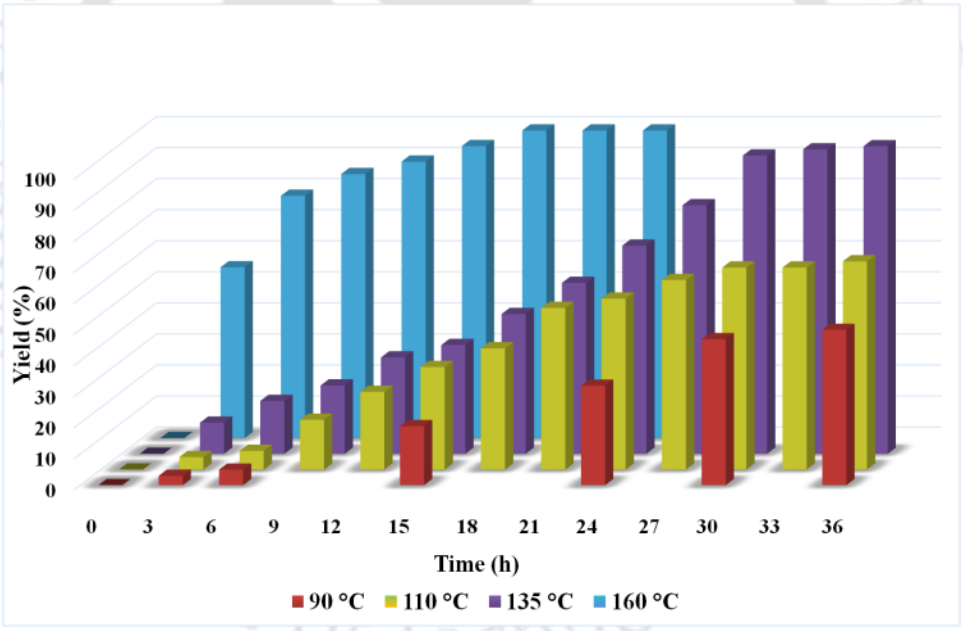

Figure 5.2: Temperature-dependent product distribution in *β*-methylation of 2-phenylethanol with methanol catalyzed by complex **2.1A**. (NMR yield)

Next, the time dependent product distribution of the catalytic reaction of *β*-methylation of 2-phenylethanol (Figure **5.1**) have been studied. The concentrations of substrate (2-phenylethanol **5.4a**) gradually decreased with time, and concurrently, the concentration of product **5.5a** increased at 135 °C. From the curve, it is clear that very slow conversion of 2-phenylethanol happened with the optimum reaction conditions, and

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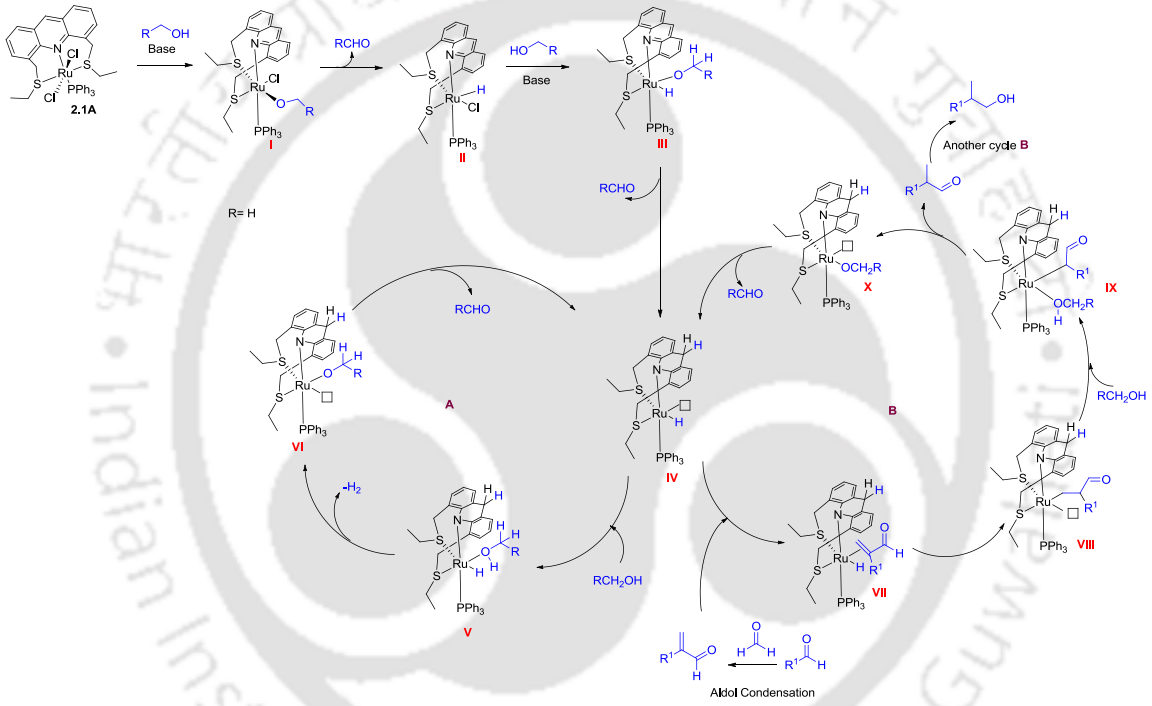
it takes 30 h to complete the reaction (Figure **5.2**). During the reaction no other intermediate have been found. At temperature 90 °C, 110 °C and 135 °C, the reaction proceeded slowly and steadily, whereas, at a higher temperature (160 °C), a sharp rise in product formation was observed. Within 3 h, 55% conversion was noticed, and it took only 15 h to complete the reaction. Therefore, the high temperature has some salient effect on product distribution over time.

5.2.4. Plausible catalytic cycle for *β*-methylation of 2-phenylethanol .



Scheme 5.15: Catalytic cycle of the plausible reaction mechanism

We proposed a probable mechanism for the *β*-methylation of 2-phenylethanol as shown in Scheme **5.15**. In the initial step, in presence of base and addition of alcohol, complex **2.1A** is converted ruthenium hydride species (**IV**) and the corresponding carbonyl compound. After that, alcohol coordination happened to the ruthenium centre and form the complex **V**. After that removal of H_2 and aldehyde molecule, complex **IV** is regenerated and the cycle will continued. Complex **IV** reduces the aldol product,

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unsaturated aldehyde *via* coordination and insertion into the Ru-H bond afforded *β*-methylated product of 2-phenylethanol.

5.2.5. Substrate scope for the to synthesize 1,1′-methylene-bis(2-naphthol):

To expand the scope of methanol activation, next, I was interested in investigating the reactivity of methanol with *β*-naphthol to synthesize 1,1′-methylene-bis(2-naphthol). These compounds frequently occur in various biologically active compounds[26] and are used as versatile synthetic intermediates and anion receptors.[26a] 1,1′-Methylene-di-(2-naphthol) radiolabelled with carbon-11 (ST1859) also used as a drug for the treatment of Alzheimer's disease.[27] Kirchner group showed the possibility (one example) of the formation of 1,1′-methylene- *bis*(2-naphthol) in their work on three-component aminomethylation reaction of 2-naphthol.[28] Herein, this protocol have been applied to synthesize several important 1,1′-methylene-bis(2-naphthol) derivatives. When 2-naphthol (1 mmol), ^{t}BuOK (1 mmol), MeOH (1 mL), and cat. **2.1A** (1 mol%) were refluxed in Ace pressure tube at 135 °C for 36 h, 1,1'-methylenebis(naphthalen-2-ol) **5.8a** was isolated in 81% yield (Scheme **5.16**). 2-Naphthol with electron donating group like 7-methoxynaphthalen-2-ol and 3-methoxynaphthalen-2-ol were also participated well in the reaction and produced 1,1'-methylenebis(7-methoxynaphthalen-2-ol) **5.8b** and 1,1'-methylenebis(3-methoxynaphthalen-2-ol) **5.8c** in good yields. Electron withdrawing groups like 6-bromo and 7-bromo napthalen-2-ol gave moderate to good yields (**5.8d**, 55% & **5.8e**, 79%).

Gram-scale synthesis of 1,1'-methylenebis(naphthalen-2-ol) with catalyst loading 0.5 mol%, using MeOH 2 mL, giving 69% isolated yield. The green chemistry metrics for this reaction with an E-factor of 2.24, 94% atom economy, 65% atom efficiency, 100% carbon efficiency, and 65% reaction mass efficiency clearly exposed the synthetic utility of this methodology (Scheme **5.17**).

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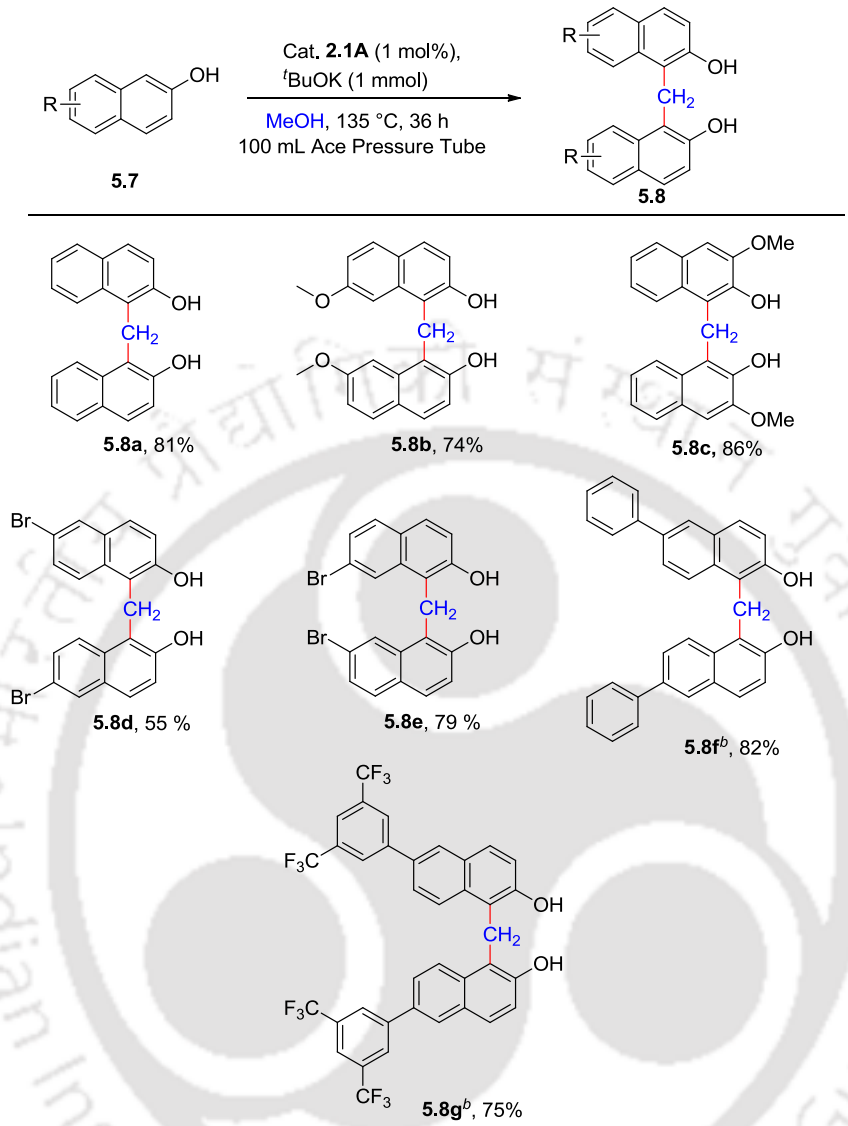
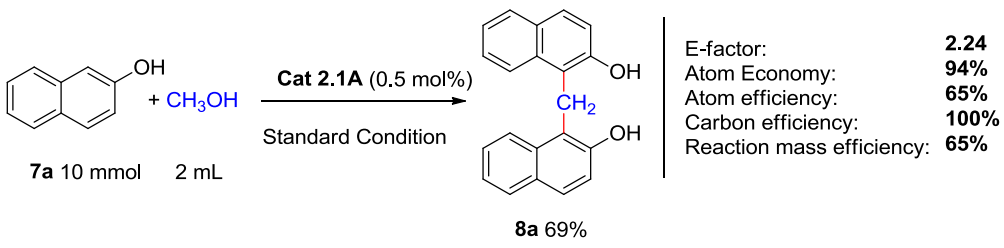


Scheme 5.16: Substrate scope for 1,1′-methylene-bis(2-naphthol).[a] [a] Reaction conditions: 2-naphthol (1 mmol), cat. **2.1A** (1 mol%), ^{t}BuOK (1 mmol), MeOH (1 mL), 36 h, 135 °C, 100 mL Ace pressure tube. [b] 0.5 mmol scale.



Scheme 5.17: Green chemistry metrics

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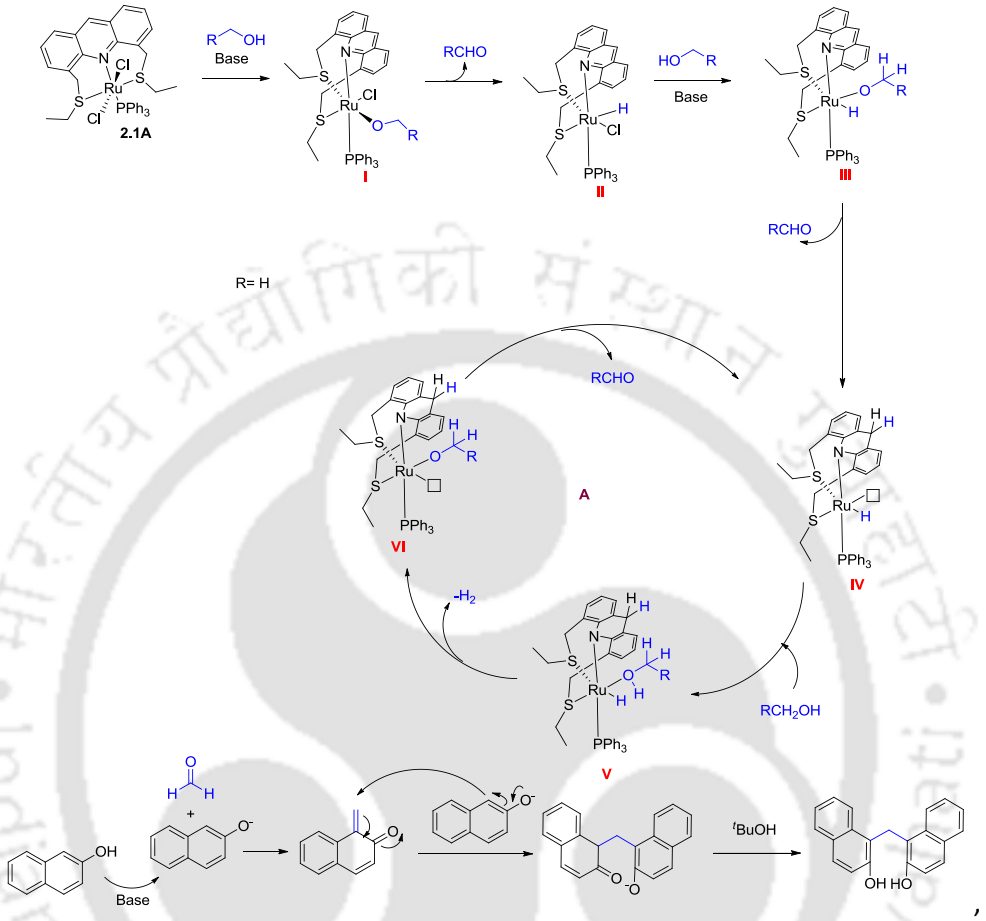
5.2.6. Plausible catalytic cycle for the synthesize of 1,1′-methylene-bis(2-naphthol).



Scheme 5.18: Catalytic cycle of the plausible reaction mechanism

We proposed a probable mechanism for synthesis of 1,1′-methylene-bis(2-naphthol) in presence of methanol as shown in Scheme **5.18**. In the initial step, in presence of base and addition of alcohol, complex **2.1A** is converted ruthenium hydride species (**IV**) and the corresponding carbonyl compound. After that, alcohol coordination happened to the ruthenium centre and forms the complex **V**. After that removal of H_2 and aldehyde molecule, complex **IV** is regenerated and the cycle will continued. Next, the nucleophilic addition reaction between formaldehye and beta naphthol derivative afforded 1,1′-methylene-bis(2-naphthol).

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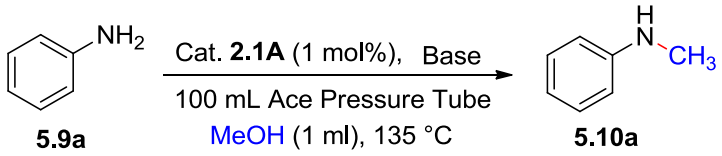
5.2.7. Optimization of the reaction condition for the methylation of amine.[a]

Table 5.2. Optimization of the reaction condition for the methylation of amine.[a]



5.9a **5.10a**

Entry	Cat. **2.1A**	Base (mmol)	Time (h)	Yield (%)[b]
1	1 mol %	KOH (0.5 mmol)	48	50
2	1 mol %	KOH (1 mmol)	48	70
3	1 mol %	KOH (2 mmol)	48	95
4	1 mol %	^{t}BuOK (1 mmol)	48	96
5	1 mol %	^{t}BuOK (1 mmol)	36	95
6	1 mol %	^{t}BuOK (0.5 mmol)	48	40
7	1 mol %	^{t}BuOK (1 mmol)	24	62
8	1 mol %	^{t}BuONa (1 mmol)	36	65
9	1 mol %	K_2CO_3 (1 mmol)	36	-
10	1 mol %	Na_2CO_3 (1 mmol)	36	-
11	0.5 mol %	^{t}BuOK (1 mmol)	48	55

[a] Reaction conditions: aniline (1 mmol), cat **2.1A** (1 mol%), base (1 mmol), MeOH (1 mL), 135 °C, 100 mL Ace pressure tube, [b] Isolated yield.

When a mixture of aniline (1 mmol), KOH (0.5 mmol), cat. **2.1A** (1 mol%) and MeOH were refluxed at 135 °C in 100 mL Ace pressure tube for 48 h, 50%, *N*-methylaniline (**5.10a**) (Table **5.2**, entry **1**) were formed. The reaction is selective toward mono-methylation as no *N*,*N*-dimethyl aniline was not detected. The yield of **5.10a** was further improved to 95% when the base amount was increased to 2 mmol (Table **5.2**,

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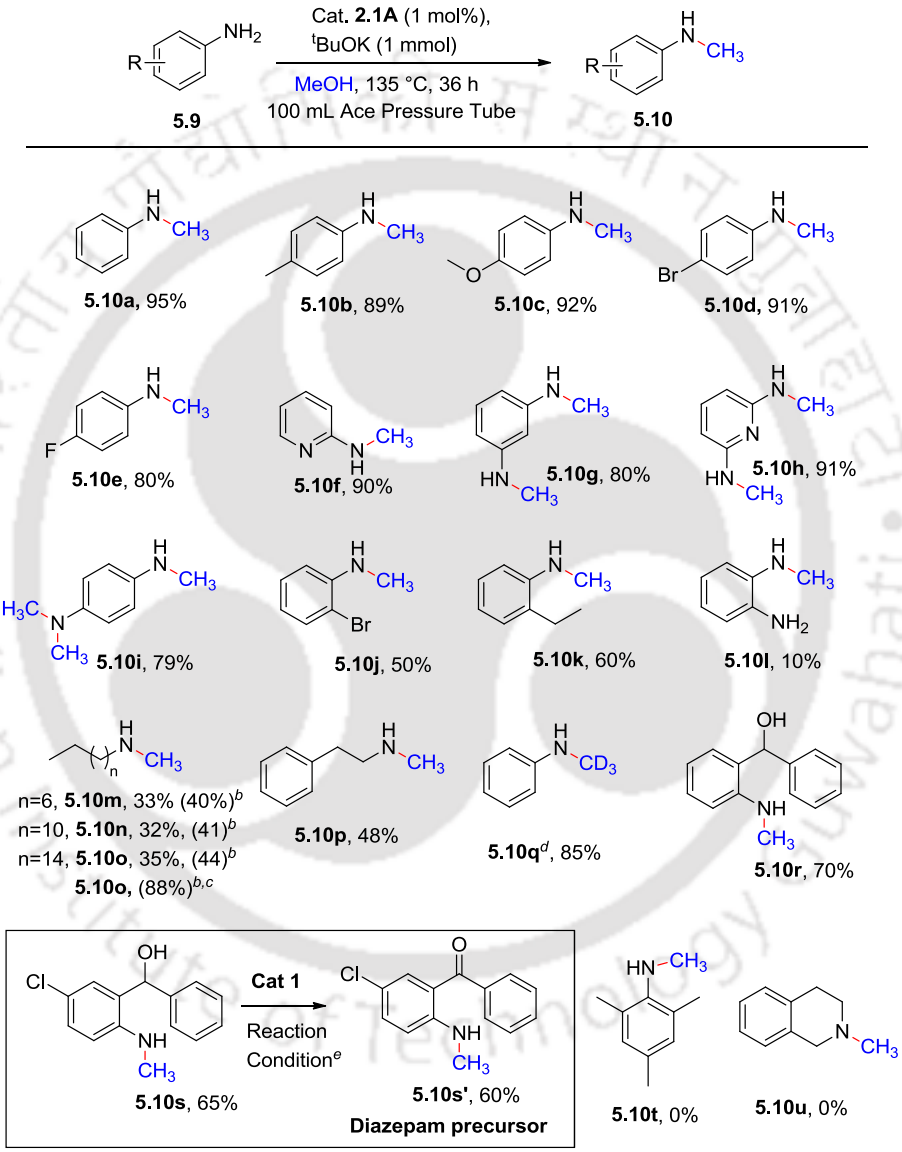
entry **3**). A quick screening of different bases (Table **5.2**, entries **4**, **5**, **8-10**) revealed that ^{t}BuOK is the better choice over KOH.

5.2.8. Substrate scope for the methylation of amine:



Scheme 5.19. Substrate scope for methylation of amine.[a a] Reaction conditions: aniline (1 mmol), cat **2.1A** (1 mol%), ^{t}BuOK (1 mmol), MeOH (1 mL), 135 °C, 36 h, 100 mL Ace pressure tube. [b]Yield in the parenthesis NMR yield. [c]5 mol% catalyst. [d]48 h. [e]**5.10p** (0.5 mmol), cat. **2.1A** (1 mol%), ^{t}BuOK (5 mol%), toluene (1 mL), 135 °C, 24 h, argon.

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After having the optimized reaction condition, the substrate scope of *N*-methylation reaction has been explored (Scheme **5.19**). Aniline with electron-donating and electron-withdrawing group were responded well giving excellent yields (80-92%) of the corresponding products (**5.10b**-**5.10e**). 2-Aminopyridine was also well-tolerated and afforded 90% yield **5.10f**. Benzene-1,3-diamine and pyridine-2,6-diamine were also converted to corresponding methylted product N^1,N^3-dimethylbenzene-1,3-diamine (**5.10g**, 80%) and N^2,N^6-dimethylpyridine-2,6-diamine (**5.10h**, 91%) in good yields. Furthermore, when two -NH_2 groups are para to each other in aromatic ring, then double methylation occur in one amine group, and mono methylation occurs on the other amine group, giving N^1,N^1,N^4-trimethylbenzene-1,4-diamine **5.10i** (79%). Substituents at the *ortho* position suppressed the product yield (**5.10j**-**5.10l**) due to the steric effect. More sterically demanding 2,4,6-trimethylaniline did not respond toward this reaction. Only moderate yields of the monomethylated products were isolated (32-35%) when aliphatic amines such as octylamine, dodecylamine and hexadecylamine were used as substrates. Under the optimized reaction conditions in presence of 1 mol% cat **2.1A**, hexadecylamine converted to the corresponding monomethylated product **5.10o** in 44% yield (35% isolated) whereas no dimethylated product was detected. Interestingly, when 5 mol% cat **2.1A** was used, 88% conversion (NMR) to the monomethylated product was observed with a small amount (8%) of dimethylated product. Furthermore, when monomethylated product **5.10o** was separately treated with MeOH under the optimized reaction condition in presence of 2 mol% cat **2.1A** only 10% dimethylated product was formed. When secondary amines such 1,2,3,4-tetrahydroisoquinoline subjected towards the methylation reaction no methylated tertiary amine (**5.10u**) was observed. When (2-aminophenyl)(phenyl)methanone and (5-chloro-2-(methylamino)phenyl)(phenyl)methanol was used as substrates, **5.10r** and **5.10s** was obtained in 70% and 65% yield respectively. Here, the carbonyl group was also hydrogenated due to the presence of excess H_2 in the reaction medium. Nevertheless, employing dehydrogenative reaction conditions using cat **2.1A**, **5.10s** can be easily converted to biologically important[29] diazepam precursor (**5.10s′**) with 60% isolated yield.

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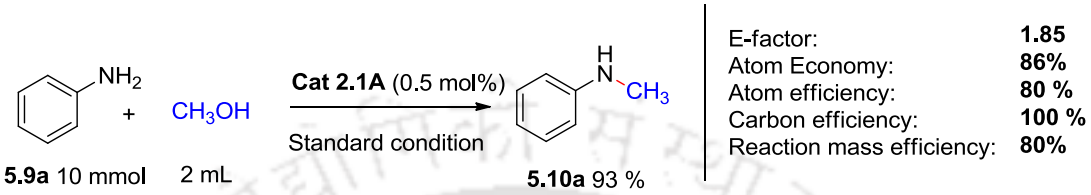
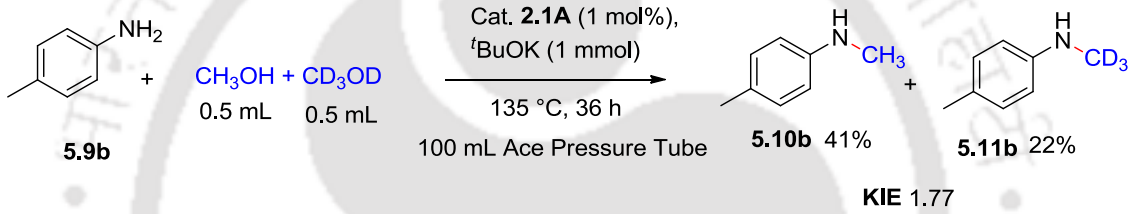
For the preparative scale synthesis of *N*-methylaniline, the green chemistry metrics with an E-factor of 1.85, 86% atom economy, 80% atom efficiency, 100% carbon efficiency, and 80% reaction mass efficiency clearly exposed the technical and environmental benefits of this methodology (Scheme **5.20**).



Scheme 5.20: Green chemistry metrics



Scheme 5.21: Labelling experiments with deuterated methanol

In order to gain insight, kinetic isotope experiments (KIE) were carried out (Scheme **5.21**). First, a mixture of CD_3OD/CH_3OH (1:1, v:v) was used in a competitive experiment. In a 100 mL Ace pressure tube, a mixture of CD_3OD (0.5 mL) and CH_3OH (0.5 mL) was reacted with *p*-toluidine under standard conditions. The observed product ratio of the deuterated and non-deuterated products was determined by ^1H NMR, which indicates the KIE value ~1.77.

5.2.9. Plausible catalytic cycle for the methylation of amine.

We proposed a probable mechanism for the methylation of amine as shown in Scheme **5.22**. In the initial step, in presence of base and addition of alcohol, complex **2.1A** is converted ruthenium hydride species (**IV**) and the corresponding carbonyl compound. After that, alcohol coordination happened to the ruthenium centre and form the complex **V**. After that removal of H_2 and aldehyde molecule, complex **IV** is

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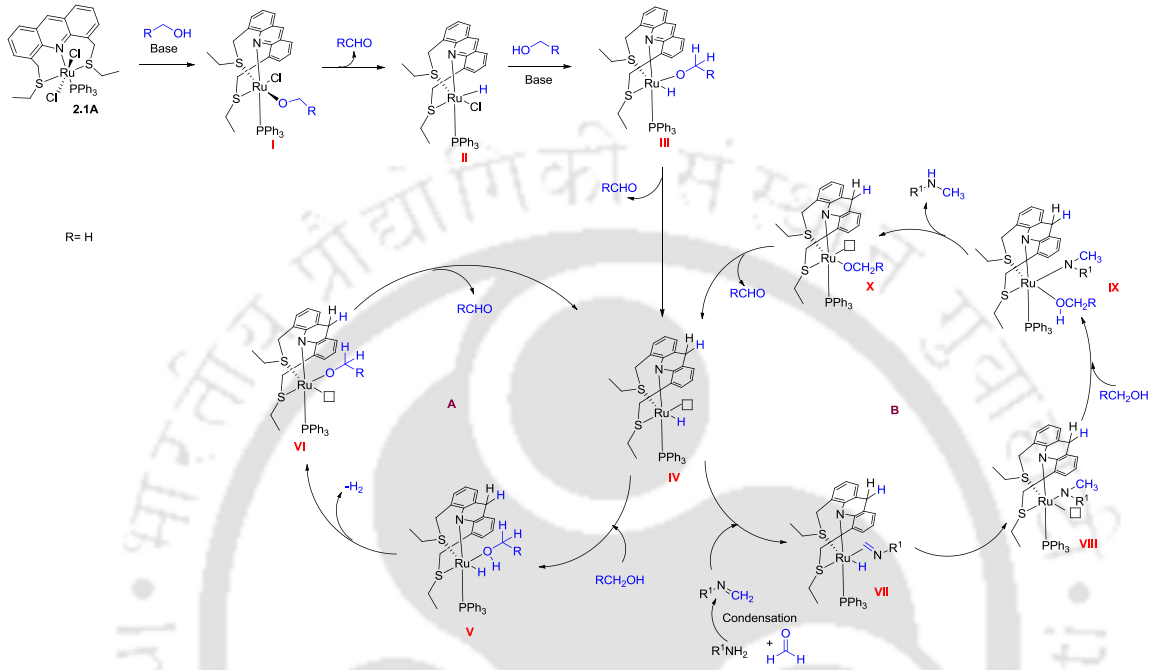
regenerated and the cycle will continued. Complex **IV** reduces unsaturated product *via* imine coordination and insertion into the Ru-H bond and afforded 2-methylaniline derivative.



Scheme 5.22: Plausible catalytic cycle for the methylation of amine.

5.3. Conclusion:

In summary, an acridine-derived air-stable ruthenium pincer complex catalyzed (1) the *β*-methylation of 2-aryllethanol, and (2) *N*-methylation of amines using methanol as a C1 building block *via* the borrowing hydrogen approach have been developed. In addition, dehydrogenative dimerization of 2-naphthol *via* methylene linkage was also illustrated. This straightforward protocol applies to a wide range of substrates giving well to excellent isolated yield. Kinetics and mechanistic investigation helps to know the reaction pathway. A temperature dependent kinetic profile *β*-methylation of 2-phenylethanol is also demonstrated. The technical and environmental benefit of this methodology was revealed, which clearly shows high atom economy and atom efficiency and 100% carbon efficiency.

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5.4. Experimental section:

General information:

Unless otherwise mentioned, all chemicals were purchase from common commercial sources and used as received. $RuCl_2(PPh_3)_3$ was purchased from Sigma-Aldrich. All solvents were dried by standard procedure.[30] Solvents such as MeOH are typically dried by heating over iodine activated magnesium and storage of the methanol over 20% m/v 3 A˚ molecular sieves. The catalyst preparation was carried out under argon atmosphere with freshly distilled dry THF or dichloromethane. All catalytic reactions were carried out under argon atmosphere using dry glassware and standard syringe/septa techniques. DRX-400 Varian and Bruker Avance III 600 and 400 spectrometers were used to record ^1H, ^{13}C NMR and ^{31}P NMR, respectively. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane; spin-spin coupling constants (*J*) are expressed in Hz and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, and br s = broad singlet. Column chromatography was done with SRL silica gel 100-200 mesh. Analytical thin layer chromatography (TLC) was carried out on silica gel plates (silica gel 60 F_{254}), that were visualized by exposure to ultraviolet light and an aqueous solution of *p*-anisaldehyde. Compounds **5.4a**, **5.7a**, **5.7c**, **5.7d**, **5.7e** and **5.9a-5.9q** were commercially available. Compounds **5.4b-5.4n**[31a] were known compound synthesized from corresponding phenyl acetic acid derivatives according to the literature procedure. **5.4ae**,[31b] **5.4ac**,[31c] **5.4ad**,[31d] **5.7b**[31e] and **5.7f-5.7g**[31f] were also synthesized following the literature procedure.

1. **General procedure for the *β*-C(sp^3)-methylation of 2-phenylethanol derivatives:**

2-phenylethanol (1 mmol), MeOH (1 mL), ^{t}BuOK (1 mmol) and complex **2.1A** (15.2 mg, 0.02 mmol) were placed in a 100 mL Ace pressure tube under argon atmosphere. The tube was sealed with screw cap and then it was immersed in an oil bath at 135 °C and stirred at this temperature for 36 h. After that, the reaction mixture was cooled to room temperature, diluted with dichloromethane, and filtered over a plug of celite. The solvent was evaporated under reduced pressure and the residue obtained was purified by

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column chromatography (Hexane:Ethylacetate 50:1) on silica gel to afford the desired product.

2. General procedure for the methylation of 2-naphthol:

2-Naphthol (1 mmol), MeOH (1 mL), ^{t}BuOK (1 mmol) and complex **2.1A** (7.6 mg, 0.01 mmol) were placed in a 100 mL Ace pressure tube under argon atmosphere. The tube was sealed with screw cap and then it was immersed in an oil bath at 135 °C and stirred at this temperature for 36 h. After that, the reaction mixture was cooled to room temperature, diluted with dichloromethane, and filtered over a plug of celite. The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (Hexane:Ethylacetate) on silica gel to afford the desired product.

3. General procedure for the methylation of amines:

Aniline (1 mmol), MeOH (1 mL), ^{t}BuOK (1 mmol) and complex **2.1A** (7.6 mg, 0.01 mmol) were placed in a 100 mL Ace pressure tube under argon atmosphere. The tube was sealed with screw cap and then it was immersed in an oil bath at 135 °C and stirred at this temperature for 36 h. After that, the reaction mixture was cooled to room temperature, diluted with dichloromethane, and filtered over a plug of celite. The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (Hexane:Ethylacetate:Triethylamine 50:1:1) on silica gel to afford the desired product.

4. Isotopic labeling experiments for *N*-methylation reaction:

Competition reaction: Aniline (1 mmol), MeOH (0.5 mL), CD_3OD (0.5 mmol), ^{t}BuOK (1 mmol) and complex **2.1A** (7.6 mg, 0.01 mmol) were placed in a 100 mL Ace pressure tube under argon atmosphere. The tube was sealed with screw cap and then it was immersed in an oil bath at 135 °C and stirred at this temperature for 36 h. After that, the reaction mixture was cooled to room temperature, diluted with dichloromethane, and filtered over a plug of Celite. The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (Hexane:Ethylacetate:Triethylamine 50:1:1) on silica gel to afford the mixture of **5.10b** & **5.11b** in 63 % yield.

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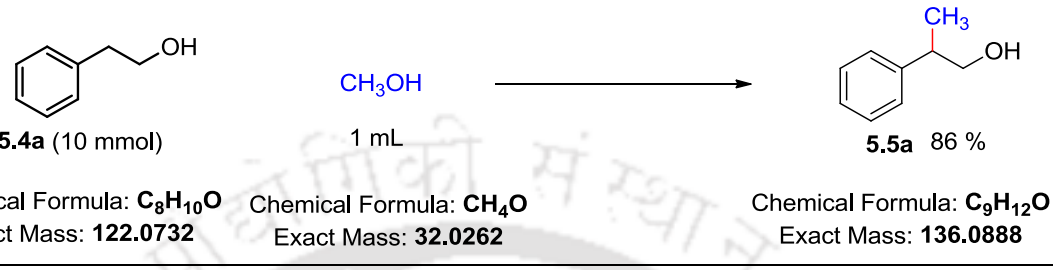
5. Evaluation of green chemistry metrics:

1. *β*-methylation of 2-phenylethanol:



5.4a (10 mmol) — **5.5a** 86 %

Chemical Formula: $C_8H_{10}O$
Exact Mass: **122.0732**

Chemical Formula: CH_4O
Exact Mass: **32.0262**

Chemical Formula: $C_9H_{12}O$
Exact Mass: **136.0888**

5.4a	CH_3OH	^tBuOK	Recycle CH_3OH	**Product (5.5a)**
1.220 g	0.792 g	1.122 g	0.396 g	1.170 g
Total= 3.134 g				

1. **E Factor** = [3.134 g - (1.170 g + 0.396 g)] ÷ 1.170 g = 1.568 g ÷ 1.170 g = **1.34** kg waste/1 kg product

2. **Atom economy** = [136.089 g ÷ (122.073 g + 32.026 g)] × 100% = **88.31%**

3. **Atom efficiency** = 86 × (88.31 ÷ 100) = **75.94%**

4. **Carbon efficiency** = (9 ÷ 9) × 100 = **100%**

5. **Reaction mass efficiency** = [1.170 g ÷ (1.220 g + 0.320 g)] × 100 = **75.97%**

2. Dimerization of 2-naphthol via methylene linkage:

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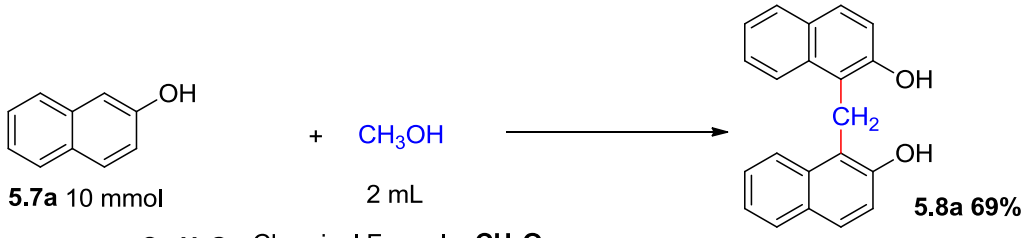

5.7a 10 mmol | 2 mL | **5.8a 69%**

Chemical Formula: $C_{10}H_8O$ | Chemical Formula: CH_4O | Chemical Formula: $C_{21}H_{16}O_2$

Exact Mass: **144.0575** | Exact Mass: **32.0262** | Exact Mass: **300.1150**

5.7a	**CH_3OH**	**^tBuOK**	**Recycle CH_3OH**	**Product (5.8a)**
1.440 g	1.584 g	1.122 g	0.792 g	1.035 g

Total= 4.146 g

1. **E Factor** = [4.146 g - (1.035 g + 0.792 g)] ÷ 1.035 g = 2.319 g ÷ 1.035 g = **2.24** kg waste/1 kg product
2. **Atom economy** = [300.115 g ÷ {(2×144.057 g) + 32.026 g}] × 100 % = **93.74%**
3. **Atom efficiency** = 69 × (93.74 ÷ 100)% = **64.68%**
4. **Carbon efficiency** = (21 ÷ 21) × 100% = **100%**
5. **Reaction mass efficiency** = [1.035 g ÷ (1.440 g + 0.16 g)] × 100 = **64.68%**

3. *N*-Methylation of amines:

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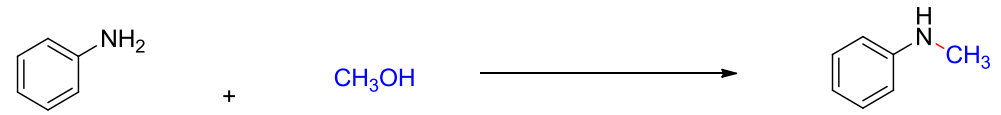

5.9a, 10 mmol + CH_3OH 2 mL → **5.10a, 93 %**

Chemical Formula: **C_6H_7N** Exact Mass: **93.0578**

Chemical Formula: **CH_4O** Exact Mass: **32.0262**

Chemical Formula: **C_7H_9N** Exact Mass: **107.0735**

5.9a	CH_3OH	^{t}BuOK	Recycle CH_3OH	Product (5.10a)
0.931 g	1.584 g	1.122 g	0.792 g	0.996 g
	Total= 3.637 g			

1. **E Factor** = [3.637 g - (0.996 g + 0.792) g] ÷ 0.996 g = 1.849 g ÷ 0.996 g = **1.85** kg waste/1 kg product
2. **Atom economy** = [107.073 g ÷ (93.057 g + 32.026 g)] × 100% = **85.60%**
3. **Atom efficiency** = 93 × (85.60 ÷ 100)% = **79.60%**
4. **Carbon efficiency** = (7 ÷ 7) × 100% = **100%**
5. **Reaction mass efficiency** = [0.996 g ÷ (0.931 g + 0.320 g)] × 100 = **79.62%**

5.5. Characterization data of products:

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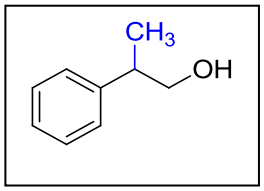
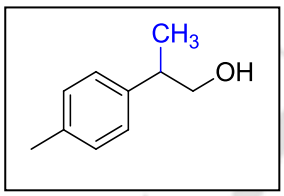
2-Phenylpropan-1-ol (5.5a):[12a]



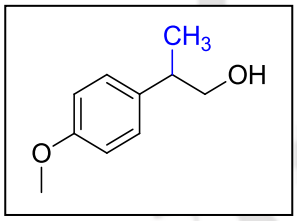
Pale yellow oil. Yield: 90%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32-7.29 (m, 2H), 7.22-7.19 (m, 3H), 3.64 (d, *J* = 7.3 Hz, 2H), 2.94-2.86 (m, 1H), 1.95 (br s, 1H), 1.25 (d, *J* = 7.1 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 143.9, 128.5 (2C), 127.5 (2C), 126.5, 68.5, 42.4, 17.6.

2-(p-Tolyl)propan-1-ol (5.5b): [12d]



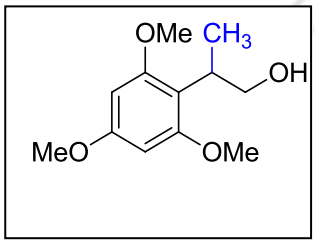
Yellow oil. Yield: 87%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16-7.13 (m, 4H), 3.69-3.67 (m, 2H), 2.94-2.90 (m, 2H), 2.34 (s, 3H), 1.39 (br s, 1H), 1.26 (d, *J* = 7.0 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 140.6, 136.3, 129.4 (2C), 127.4 (2C), 68.8, 42.1, 21.1, 17.7.

2-(4-Methoxyphenyl)propan-1-ol (5.5c):[12a]



Yellow oil. Yield: 81%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 3.66-3.64 (m, 2H), 2.92-2.88(m, 1H), 1.71 (br s, 1H), 1.24 (d, *J* = 7.0 Hz, 2H).^{13}C NMR (150 MHz, $CDCl_3$) δ 158.4, 135.7, 128.5 (2C), 114.1 (2C), 68.9, 55.3, 41.6, 17.8.

2-(2,4,6-Trimethoxyphenyl)propan-1-ol (5.5d):



Yellow oil. Yield: 95%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.43 (s, 2H), 3.85 (s, 6H), 3.85 (s, 3H), 3.67-3.65 (m, 2H), 2.90-2.84 (m, 1H), 1.82 (br s, 1H), 1.24 (d, J = 7.1 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 153.3, 139.5, 136.6, 104.2, 68.7, 60.9, 56.1, 42.9, 17.7. HRMS (ESI+): m/z calcd. for $C_{12}H_{19}O_4$: 227.1283 [M+H]+; Found: 227.1288.

2-(4-Chlorophenyl)propan-1-ol (5.5e):[12a]

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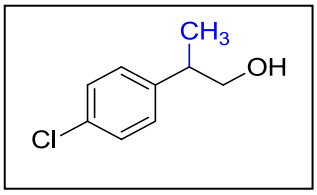
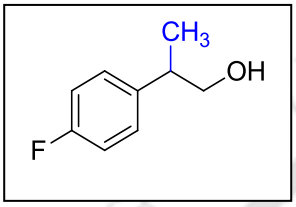


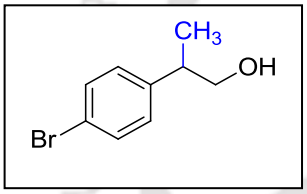
Pale yellow oil. Yield: 73%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 3.87-3.39 (m, 2H), 2.96-2.90 (m, 1H), 1.46 (br s, 1H), 1.25 (d, *J* = 7.0 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 142.3, 132.4, 128.9 (2C), 128.8 (2C), 68.6, 41.9, 17.6.

2-(4-Fluorophenyl)propan-1-ol (5.5f):[12a]



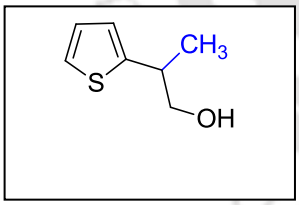
Yellow oil. Yield: 92%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20-7.16 (m, 2H), 3.64-3.61 (m, 2H), 2.95-2.86 (m, 1H), 1.85 (br s, 1H), 1.24 (d, *J* = 7.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.6 (d, *J* = 244.3 Hz), 139.5 (d, *J* = 3.2 Hz), 128.9 (d, *J* = 7.8 Hz), 115.3 (d, *J* = 21.0 Hz), 68.6, 41.7, 17.7.

2-(4-Bromophenyl)propan-1-ol (5.5g):[12d]



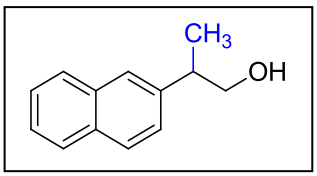
Yellow oil. Yield: 60%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 3.72-3.67 (m, 2H), 2.97-2.92 (m, 1H), 1.36 (br s, 1H), 1.28 (d, *J* = 7.0 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 142.9, 131.8, 129.3 (2C), 126.8 (2C), 68.6, 42.6, 17.6.

2-(Thiophen-2-yl)propan-1-ol (5.5h):[12d]



Yellow oil. Yield: 96%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 (d, *J* = 4.7 Hz, 1H), 6.97-6.93 (m, 1H), 6.87 (d, *J* = 3.1 Hz, 2H), 3.64 (d, *J* = 6.3 Hz, 2H), 3.23-3.19 (m, 1H), 1.33 (d, *J* = 7.0 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 147.5, 126.9, 124.0, 123.6, 69.1, 38.2, 18.7.

2-(Naphthalen-2-yl)propan-1-ol (5.5i):[12a]



Off white solid. Yield: 75%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 1.5 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.59-7.48 (m, 3H), 7.45 (d, *J* = 7.0 Hz, 1H), 3.98-3.84 (m, 3H), 1.58 (br s, 1H), 1.47 (d, *J* = 6.8 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 139.6, 134.1, 132.0, 129.1, 127.2, 126.1, 125.6 (2C), 123.1, 123.1, 68.2, 36.4, 17.9.

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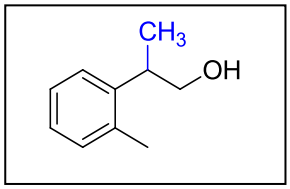
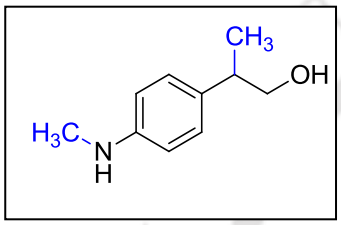
2-(o-Tolyl)propan-1-ol (5.5j): [12a]



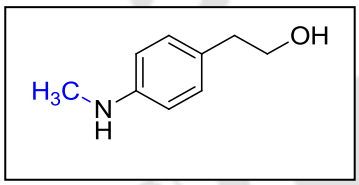
Yellow oil. Yield: 65%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22-7.11 (m, 4H), 3.76-3.67 (m, 2H), 3.29-3.24 (m, 1H), 2.37 (s, 3H), 1.62 (br s, 1H), 1.25 (d, *J* = 7.0 Hz, 1H).^{13}C NMR (150 MHz, $CDCl_3$) δ 141.8, 136.5, 130.6, 126.4, 126.3, 125.5, 68.1, 37.3, 19.7, 17.6.

2-(4-(Methylamino)phenyl)propan-1-ol (5.5l):[12d]



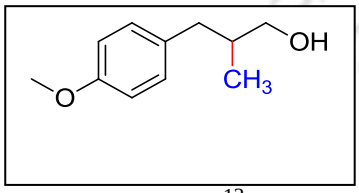
Pale yellow oil. Yield: 60%; ^{1}H NMR (600 MHz $CDCl_3$) δ 7.05 (d, *J* = 8.5 Hz, 2H), 6.60 (d, *J* = 8.5 Hz, 2H), 3.64-3.62 (m, 2H), 2.82 (s, 3H), 1.23 (d, *J* = 7.0 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 148.2, 132.1, 128.3 (2C), 112.82 (2C), 68.9, 41.6, 30.9, 17.8.

2-(4-(Methylamino)phenyl)ethanol (5.5m):[32]



Yellow oil. Yield: 10%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.4 Hz, 2H), 6.59 (d, *J* = 8.4 Hz, 2H), 3.80 (t, *J* = 6.5 Hz, 2H), 2.83 (s, 3H), 2.77 (t, *J* = 6.5 Hz, 2H).^{13}C NMR (150 MHz, $CDCl_3$) δ 148.1, 129.9 (2C), 126.8, 112.8 (2C), 64.1, 38.3, 31.0.

3-(4-Methoxyphenyl)-2-methylpropan-1-ol (5.5p):[33]



Colourless oil. Yield: 55%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 3.79 (s, 3H), 3.54-3.45 (m, 2H), 2.68 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.38 (dd, *J* = 13.6, 8.0 Hz, 1H), 1.97-1.85 (m, 1H), 0.90 (d, *J* = 6.8 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 157.9, 132.7, 130.1, 113.8, 67.8, 55.3, 38.9, 38.0, 16.5.

2-Phenylprop-2-en-1-ol (5.4ae):[34]

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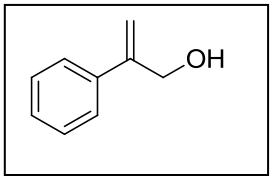
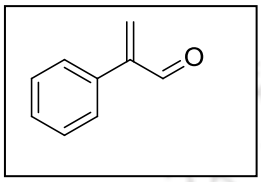


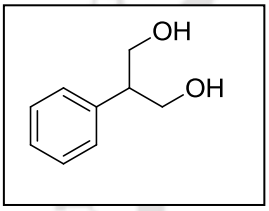
Yellow oil. Yield: 85%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 5.48 (d, *J* = 1.1 Hz, 1H), 5.36 (d, *J* = 1.4 Hz, 1H), 4.55 (s, 2H).^{13}C NMR (150 MHz, $CDCl_3$) δ 147.3, 138.5, 128.6, 128.0, 126.1, 112.7, 65.1.

2-Phenylacrylaldehyde (5.4ac): [35]



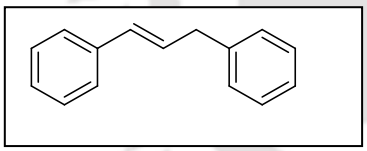
^{1}H NMR (600 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.47-7.38 (m, 1H), 6.67 (s, 1H), 6.22 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.2, 148.6, 135.8, 133.8, 128.9, 128.5, 128.2.

2-Phenylpropane-1,3-diol (4ad): [36]



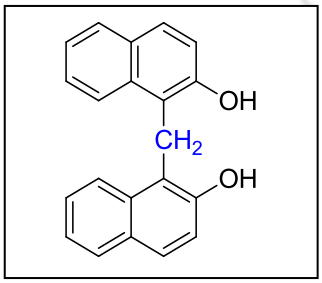
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.31 (m, 2H), 7.28-7.17 (m, 3H), 4.05-3.86 (m, 4H), 3.07 (m, 1H), 1.94 (brs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.5, 128.9 (2C), 128.2 (2C), 127.3, 66.0 (2C), 49.9.

***(E)-Prop-1-ene-1,3-diyldibenzene (5.6a'')*:** [37]



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 -7.04 (m, 10H), 6.55 (d, *J* = 15.8 Hz, 1H), 6.45 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.64 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.3, 137.6, 131.2, 129.4, 128.8, 128.6 (2C), 127.23, 126.31, 126.27, 39.48.

1,1'-Methylenebis(naphthalen-2-ol) (5.8a): [38]



White solid. Yield: 81%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.6 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.45 (t, *J* = 8.1 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.60 (br s, 2H), 4.81 (s, 2H).^{13}C NMR (150 MHz, $CDCl_3$) δ 151.6, 133.5, 129.8, 129.0, 129.0, 127.0, 123.4, 123.2, 118.1, 117.3, 21.8.

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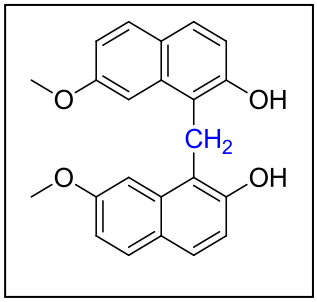
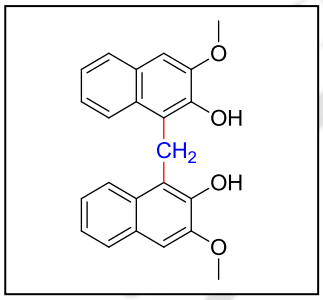
1,1'-Methylenebis(7-methoxynaphthalen-2-ol) (5.8b):



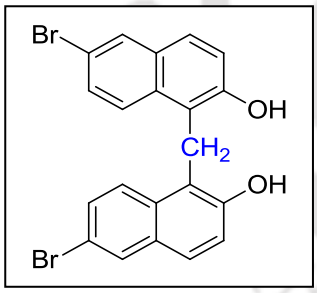
White solid. Yield: 74%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.22 (s, 2H), 7.66-7.33 (m, 6H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 4.64 (s, 2H), 3.69 (s, 6H).^{13}C NMR (150 MHz, DMSO-d_6) δ 157.1, 152.5, 135.0, 129.5, 127.2, 123.7, 118.1, 114.9, 114.5, 102.8, 54.9, 20.4. HRMS (ESI+): m/z calcd. for $C_{23}H_{21}O_4$: 361.1440 $[M+H]^+$; Found: 361.1441.

1,1'-Methylenebis(3-methoxynaphthalen-2-ol) (5.8c):



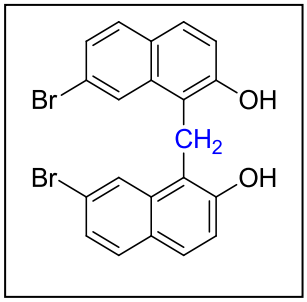
White solid. Yield: 86%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 6.3, 3.4 Hz, 2H), 7.63 (dd, *J* = 6.2, 3.3 Hz, 2H), 7.24 (dd, *J* = 6.3, 3.3 Hz, 4H), 7.04 (s, 2H), 6.61 (s, 2H), 4.88 (s, 2H), 4.04 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.9, 143.3, 129.3, 129.1, 127.2, 124.2, 123.9, 123.6, 119.1, 104.7, 56.0, 21.8. HRMS (ESI-): m/z calcd. for $C_{23}H_{20}O_4$: 359.1283 [M-H]; Found: 359.1290

1,1'-Methylenebis(6-bromonaphthalen-2-ol) (5.8d):[39]



White solid. Yield: 55%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.47 (s, 2H), 8.08 (d, *J* = 9.2 Hz, 2H), 7.93 (d, *J* = 2.1 Hz, 2H), 7.62 (d, *J* = 8.9 Hz, 2H), 7.44-7.22 (m, 4H), 4.64 (s, 2H).^{13}C NMR (150 MHz, DMSO-d_6) δ 152.4, 132.3, 130.0, 129.9, 128.4, 127.2, 126.1, 119.6, 119.4, 115.31, 20.3.

1,1'-Methylenebis(7-bromonaphthalen-2-ol) (5.8e):



White solid. Yield: 79%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.62 (s, 2H), 8.43 (s, 2H), 7.66-7.63 (m, 4H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 4.59 (s, 2H).^{13}C NMR (150 MHz, DMSO-d_6) δ 152.8, 134.9, 130.36, 127.9, 126.8, 125.9, 125.1, 119.6, 118.4, 118.2, 20.0. HRMS (ESI-): m/z calcd. for $C_{21}H_{14}Br_2O_2$: 456.9262 $[M-H]^-$; Found: 456.9268.

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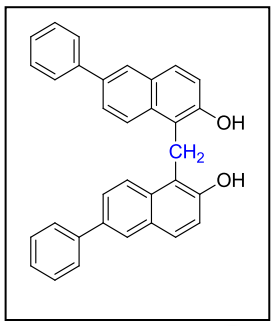
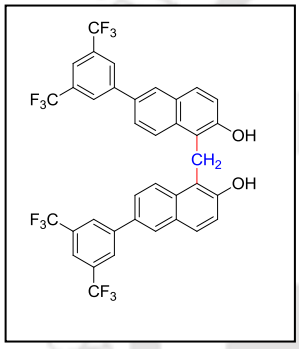
1,1'-Methylenebis(6-phenylnaphthalen-2-ol) (5.8f):



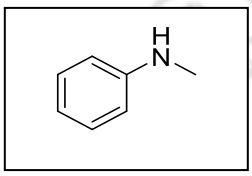
White solid. Yield: 82%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.30 (s, 2H), 8.38-8.21 (m, 2H), 7.96 (s, 2H), 7.71 (d, *J* = 11.0 Hz, 2H), 7.67 (d, *J* = 7.9 Hz, 6H), 7.51 (d, *J* = 8.9 Hz, 4H), 7.41 (t, *J* = 7.6 Hz, 6H), 7.35-7.28 (m, 4H), 4.74 (s, 2H).^{13}C NMR (150 MHz, DMSO-d_6) δ 152.1, 140.0, 133.75, 133.0, 128.9, 128.8, 128.1, 128.1, 127.0, 126.5, 125.6, 124.5, 119.38, 118.6, 20.5. HRMS (ESI-): m/z calcd. for $C_{33}H_{24}O_2$: 451.1698 [M-H]$^-$; Found: 451.1705.

1,1'-Methylenebis(6-(3,5-bis(trifluoromethyl)phenyl)naphthalen-2-ol) (5.8g):



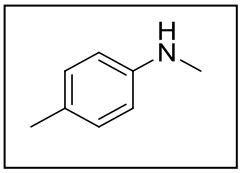
White solid. Yield: 75%; ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 10.48 (s, 2H), 8.35 (s, 4H), 8.31-8.23 (m, 4H), 8.00 (s, 2H), 7.80 (d, *J* = 8.9 Hz, 2H), 7.71 (d, *J* = 9.1 Hz, 2H), 7.37 (d, *J* = 8.9 Hz, 2H), 4.77 (s, 2H). ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 153.3, 143.0, 134.2, 131.3 (q, *J* = 32.8 Hz), 129.0 (d, *J* = 9.3 Hz), 127.5, 127.4, 126.5, 125.2, 124.7 (d, *J* = 6.5 Hz), 122.9, 121.1, 120.7, 119.8, 119.3, 20.9. HRMS (ESI-): m/z calcd. for $C_{37}H_{20}F_{12}O_2$: 723.1193 [M-H]$^-$; Found: 723.1200.

N-Methylaniline (5.10a):[18j]



Pale yellow oil. Yield: 95%;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 (t, *J* = 8.4 Hz, 2H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.65 (d, *J* = 7.7 Hz, 2H), 3.72 (br s, 1H), 2.86 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 149.4, 129.3 (2C), 117.3, 112.5 (2C), 30.8.

N,4-Dimethylaniline (5.10b):[23e]



Pale yellow oil. Yield: 89%;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.6 Hz, 2H), 6.59 (d, *J* = 8.4 Hz, 2H), 3.59 (br s, 1H), 2.85 (s, 3H), 2.30 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 147.2, 129.7 (2C), 126.5, 112.68 (2C), 31.1, 20.4.

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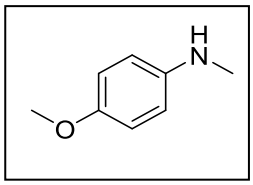
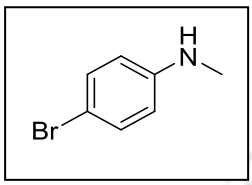
4-Methoxy-N-methylaniline (5.10c):[23e]



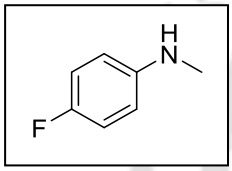
Pale yellow oil. Yield: 92%;^{1}H NMR (600 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.9 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 2H), 3.76 (s, 3H), 3.17 (br s, 1H), 2.81 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 152.2, 143.72, 115.0 (2C), 113.8 (2C), 55.9, 31.7.

4-Bromo-N-methylaniline (5.10d):[23e]



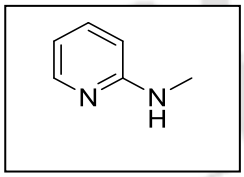
Pale yellow oil. Yield: 91%;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.9 Hz, 2H), 6.46 (d, *J* = 8.8 Hz, 2H), 3.71 (br s, 1H), 2.78 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 148.3, 131.9 (2C), 114.0 (2C), 108.8, 30.7.

4-Fluoro-N-methylaniline (5.10e):[23d]



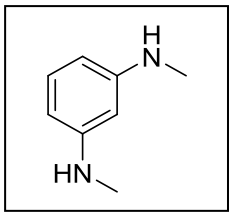
Pale yellow oil. Yield: 80%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.93-6.90 (m, 2H), 6.56-6.54 (m, 1H), 2.81 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.8 (d, *J* = 234.4 Hz), 145.8 (d, *J* = 1.8 Hz), 115.7 (d, *J* = 22.5 Hz, 2C), 113.2 (d, *J* = 7.6 Hz, 2C), 31.4.

N-Methylpyridin-2-amine (5.10f):[40]



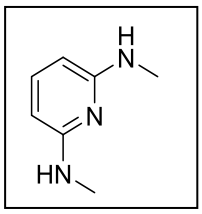
Pale yellow oil. Yield: 90%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, *J* = 4.8 Hz, 1H), 7.50-7.34 (m, 1H), 6.63-6.49 (m, 1H), 6.36 (d, *J* = 8.4 Hz, 1H), 4.70 (br s, 1H), 2.88 (d, *J* = 5.3 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 159.7, 148.2, 137.5, 112.7, 106.2, 29.1.

N^1,N^3-Dimethylbenzene-1,3-diamine (5.10g):[41]



Pale yellow oil. Yield: 80%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05-7.00 (m, 1H), 6.08-6.01 (m, 2H), 5.89 (d, *J* = 2.3 Hz, 1H), 3.61 (br s, 2H), 2.83 (s, 6H).^{13}C NMR (150 MHz, $CDCl_3$) δ 150.6 (2C), 129.9, 102.6 (2C), 96.4, 30.9 (2C).

N^2,N^6-Dimethylpyridine-2,6-diamine (5.10h):[41]



Pale yellow oil. Yield: 91%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.9 Hz, 1H), 5.73 (d, *J* = 7.9 Hz, 2H), 2.84 (d, *J* = 5.2 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2 (2C), 139.2, 94.1 (2C), 29.3 (2C).

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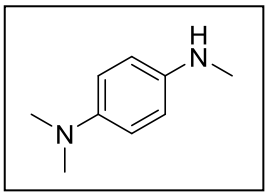
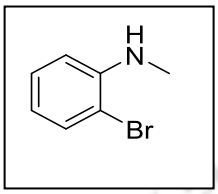
N^1,N^1,N^4-Trimethylbenzene-1,4-diamine (5.10i):[42]



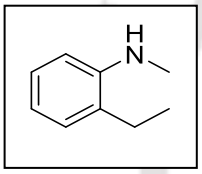
Pale yellow oil. Yield: 79%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.8 Hz, 2H), 6.63 (d, *J* = 8.8 Hz, 2H), 3.38 (br s, 1H), 2.83 (s, 6H), 2.81 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 144.2, 142.2, 116.1 (2C), 114.0 (2C), 42.5 (2C), 31.8.

2-Bromo-N-methylaniline (5.10j):[43]



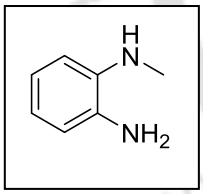
Pale yellow oil. Yield: 50%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.9 Hz, 1H), 7.25 (t, *J* = 7.7 Hz, 2H), 6.66 (d, *J* = 9.1 Hz, 1H), 6.61 (t, *J* = 8.3 Hz, 1H), 4.39 (br s, 1H), 2.93 (d, *J* = 5.2 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 146.0, 132.3, 128.6, 117.7, 110.8, 109.7, 30.7.

2-Ethyl-N-methylaniline (5.10k):[23e]

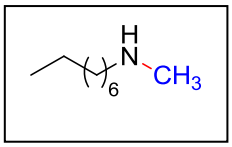


Pale yellow oil. Yield: 60%;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.7 Hz, 1H), 7.09 (m, 1H), 6.73 (t, *J* = 7.4 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 3.68 (br s, 1H), 2.90 (s, 3H), 2.49 (q, *J* = 7.5 Hz, 2H), 1.26 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.7, 127.7, 127.6, 127.1, 117.1, 109.5, 30.9, 23.8, 12.9.

N^1-Methylbenzene-1,2-diamine (5.10l):[45] Pale yellow oil. Yield: 10%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.86-6.85 (m, 1H), 6.73 -6.65 (m, 1H), 3.33 (s, 2H), 2.87 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 139.1, 134.1, 120.9, 118.5, 116.4, 111.0, 31.1.

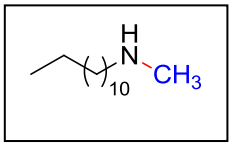


N-Methyloctan-1-amine (5.10m):[45]



Pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.57 (t, *J* = 7.4 Hz, 2H), 2.43 (s, 3H), 1.53-1.45 (m, 1H), 1.30-1.2 (m, 10H), 0.85 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 51.5, 35.6, 31.9, 29.5, 29.3, 28.9, 27.3, 22.7, 14.2.

N-Methyldodecan-1-amine (5.10n):[46]



White solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.74 (t, *J* = 7.9 Hz, 2H), 2.54 (s, 3H), 1.67-1.65 (m, 2H), 1.41-1.09 (m, 18H), 0.84 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 50.4, 34.2, 32.0, 29.7, 29.6,

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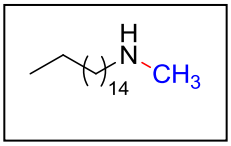
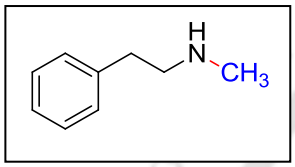
29.6, 29.4, 29.3, 27.4, 27.3, 27.0, 22.7, 14.2.

N-Methylhexadecan-1-amine (5.10o):[47]



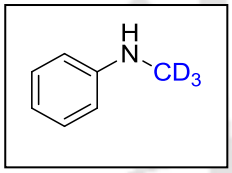
White solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.54 (t, *J* = 7.3 Hz, 2H), 2.41 (s, 3H), 1.84 (brs, 1H), 1.48-1.42 (m, 2H), 1.33-1.13 (m, 26H), 0.86 (t, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 52.2, 36.5, 32.1, 30.0, 29.8, 29.8, 29.7, 29.7, 29.5, 27.4, 22.8, 14.3.

N-Methyl-2-phenylethanamine (5.10p):[48]



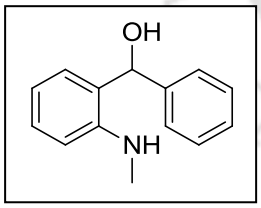
White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.24 (m, 2H), 7.22-7.16 (m, 3H), 2.97-2.95 (m, 4H), 2.53 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 128.8, 128.7, 126.7, 52.0, 34.7, 34.42.

N-(Trideuteromethyl)aniline (5.10q):[49]



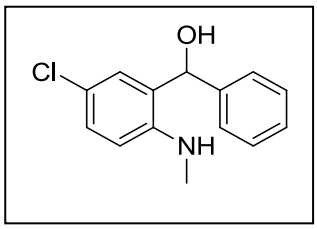
Pale yellow oil. Yield: 85%; 1H NMR (600 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.9 Hz, 2H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.65 (d, *J* = 7.7 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.4, 129.2 (2C), 117.3, 112.5 (2C), 30.3-29.8 (m).

(2-(Methylamino)phenyl)(phenyl)methanol (5.10r):[50]



Pale yellow oil. Yield: 70%; ^{1}H NMR (600 MHz, $CDCl_3$) 7.42-7.28 (m, 6H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 7.3 Hz, 2H), 5.84 (s, 1H), 2.80 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 147.7, 141.9, 129.3, 128.6, 128.5 (2C), 127.6, 126.6, 116.6, 110.9, 75.1, 30.6.

(5-Chloro-2-(methylamino)phenyl)(phenyl)methanol (5.10s):[51]



Pale yellow oil. Yield: 60%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45-7.30 (m, 5H), 7.18 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.95 (d, *J* = 2.6 Hz, 1H), 6.57 (d, *J* = 8.6 Hz, 1H), 5.75 (s, 1H), 4.53 (brs, 1H), 2.74 (d, *J* = 4.2 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 146.2, 141.2, 128.8, 128.7, 128.3, 128.2, 128.1, 126.7, 121.4, 112.0, 74.6, 30.7.

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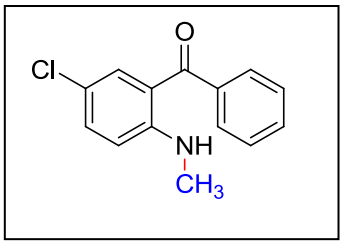
(5-Chloro-2-(methylamino)phenyl)(phenyl)methanone (5.10s'):[52]



Yellow solid. Yield 60%.^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.61 (d, *J* = 7.3 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.49-7.42 (m, 3H), 7.37 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.73 (d, *J* = 9.0 Hz, 1H), 2.98 (d, *J* = 5.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.4, 151.3, 139.9, 135.0, 134.1, 131.2, 129.1, 128.3, 118.3, 118.0, 112.85, 29.74.

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5.7. ^{1}H, ^{13}C and ^{2}H spectra of the products:

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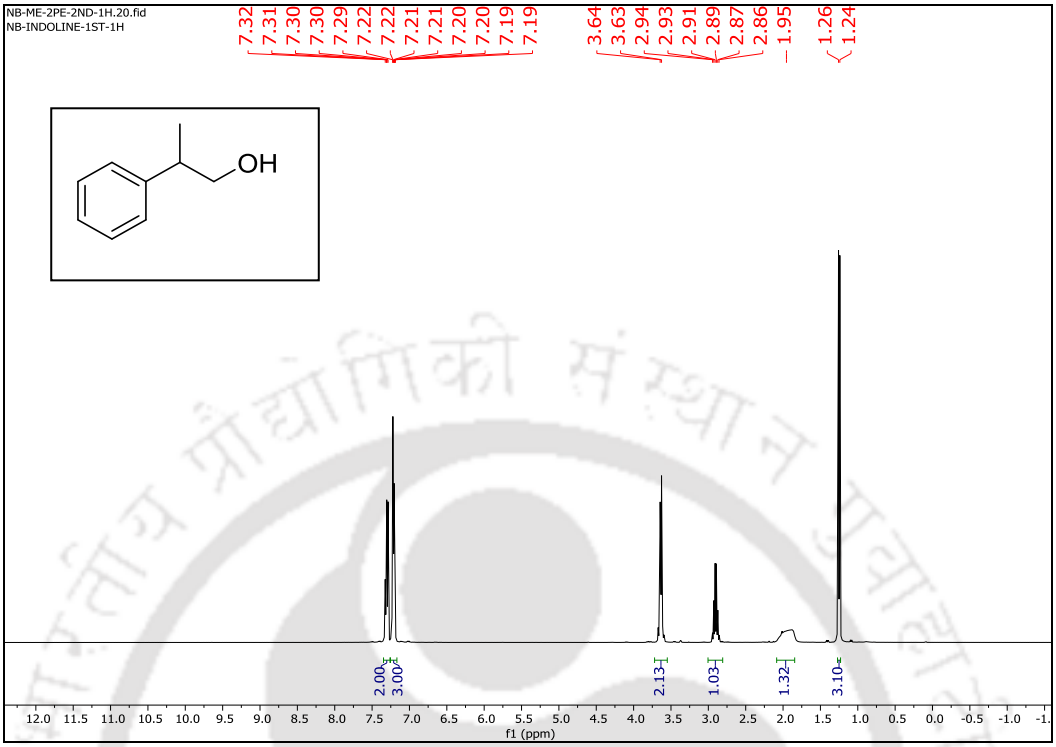

Figure 5.3: ^{1}H spectra of **5.5a** in $CDCl_3$

Figure 5.4: ^{13}Cspectra of **5.5a** in $CDCl_3$

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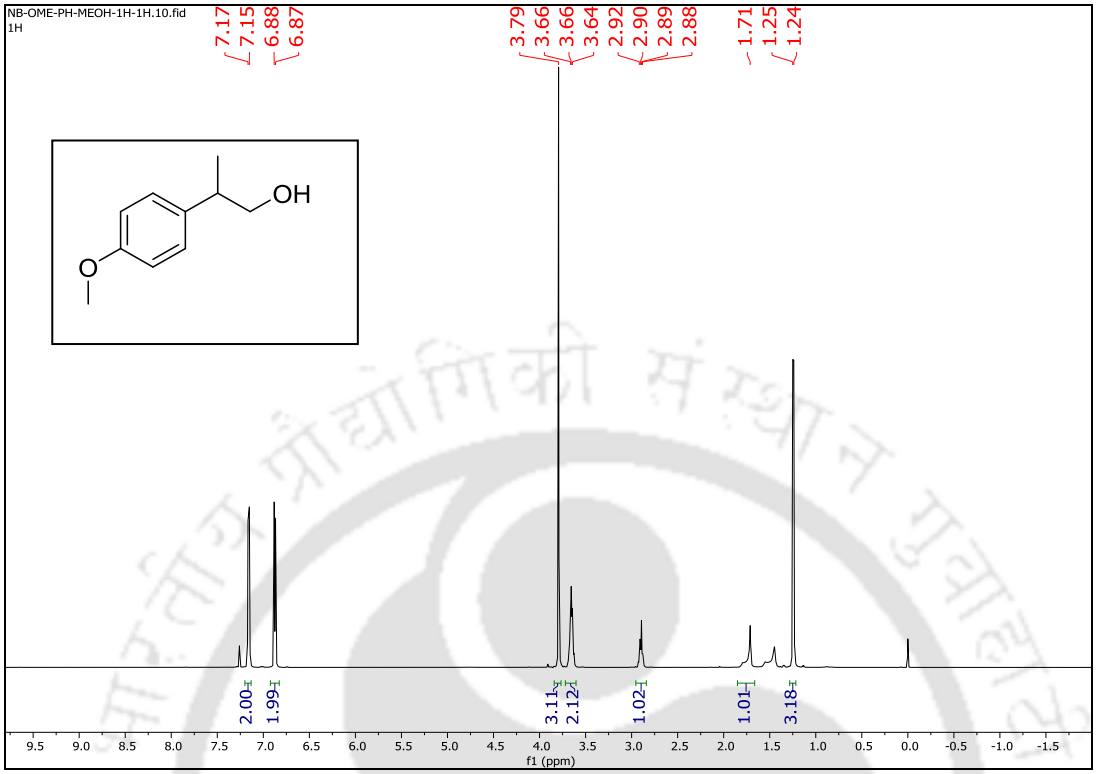

Figure 5.5: ^{1}H spectra of **5.5c** in $CDCl_3$

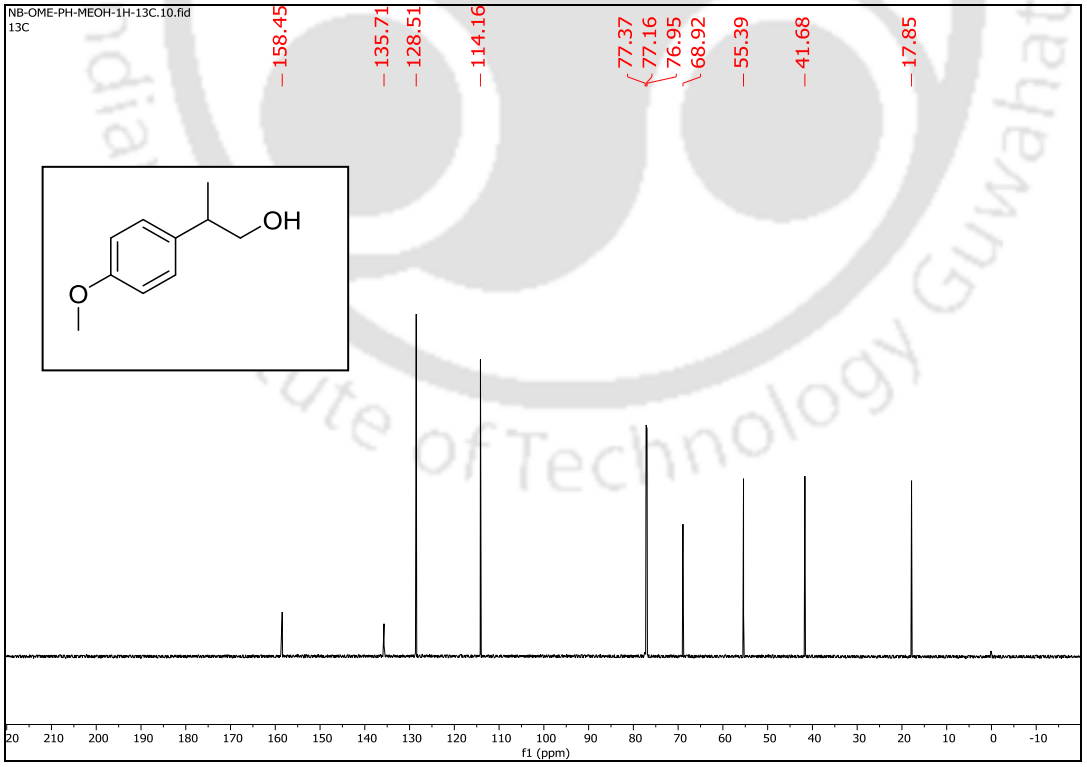

Figure 5.6: ^{13}C spectra of **5.5c** in $CDCl_3$

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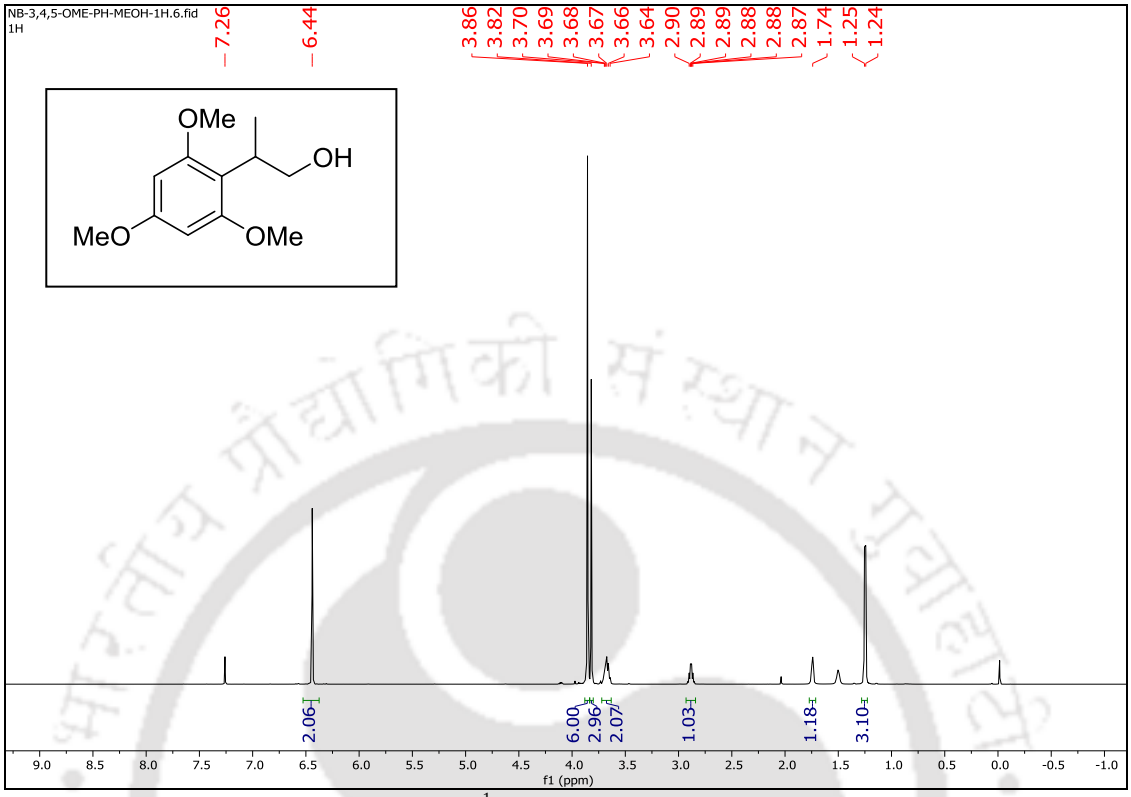

Figure 5.7: ^{1}H spectra of **5.5d** in $CDCl_3$

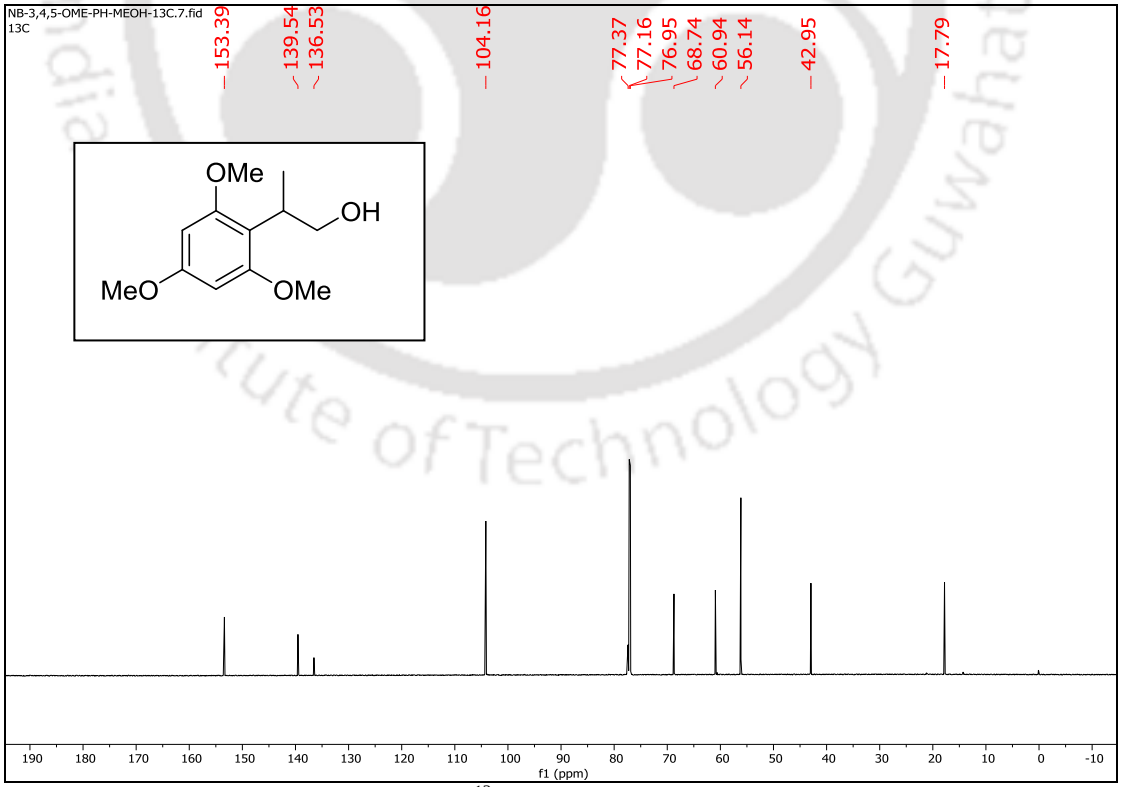

Figure 5.8: ^{13}C spectra of **5.5d** in $CDCl_3$

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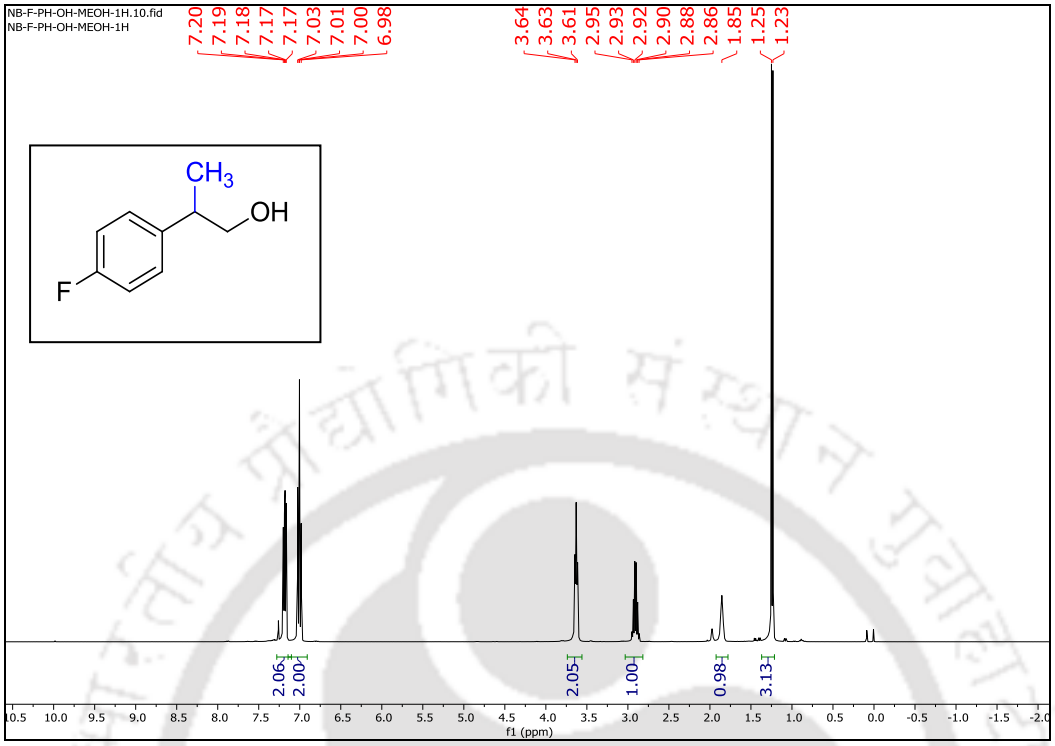

Figure 5.9: ^{1}H spectra of **5.5f** in $CDCl_3$

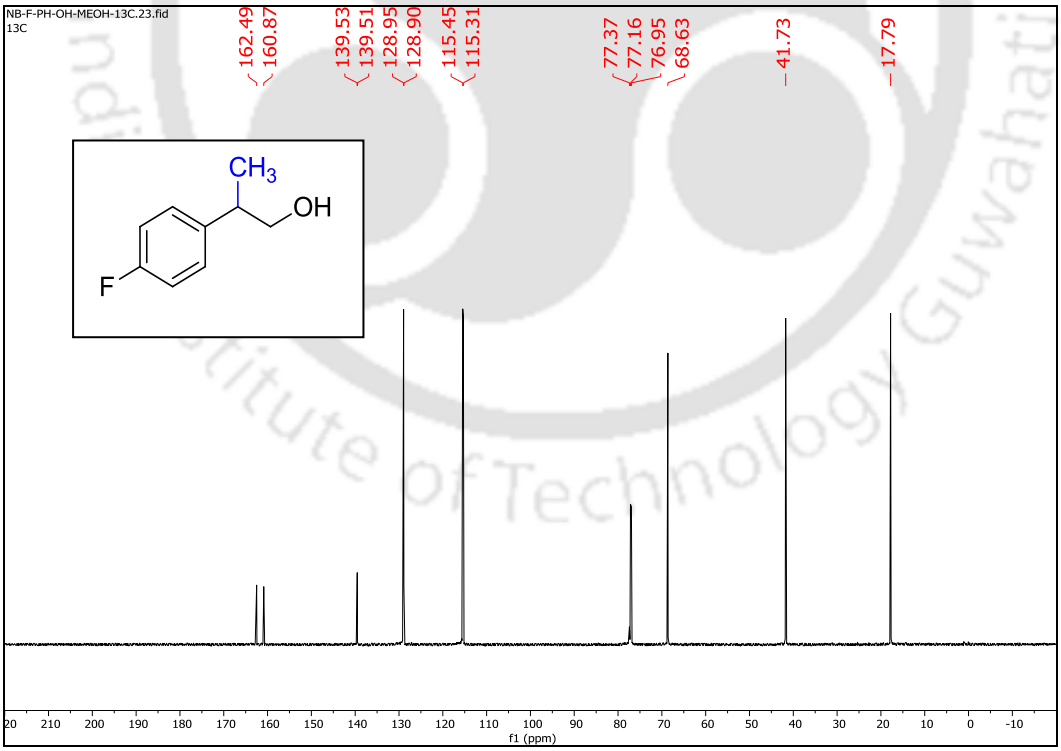

Figure 5.10: ^{13}C spectra of **5.5f** in $CDCl_3$

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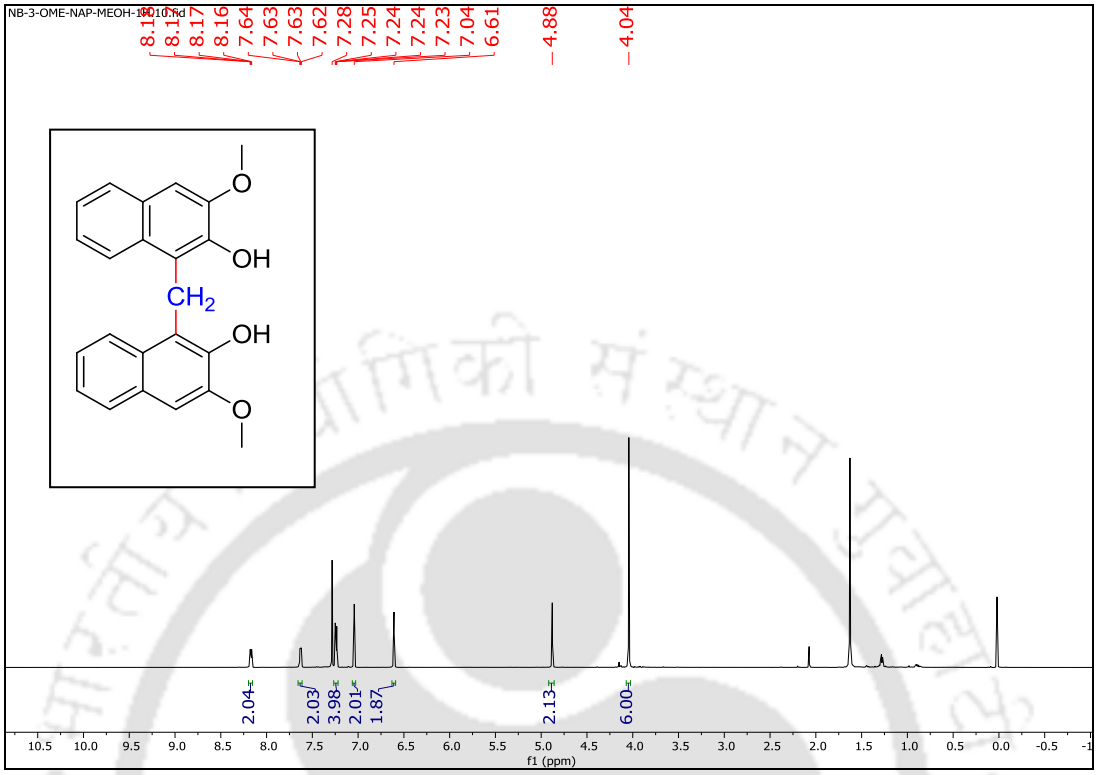

Figure 5.11: ^{1}H spectra of **5.8c** in DMSO-D_6

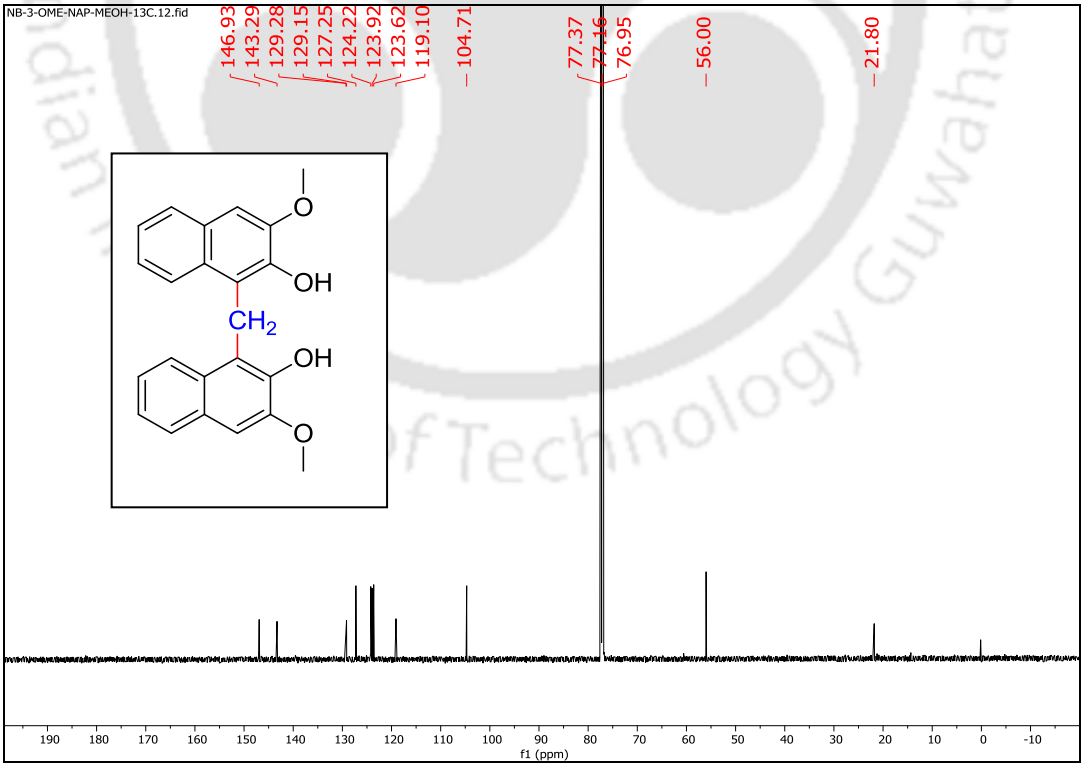

Figure 5.12: ^{13}C spectra of **5.8c** in DMSO-D_6

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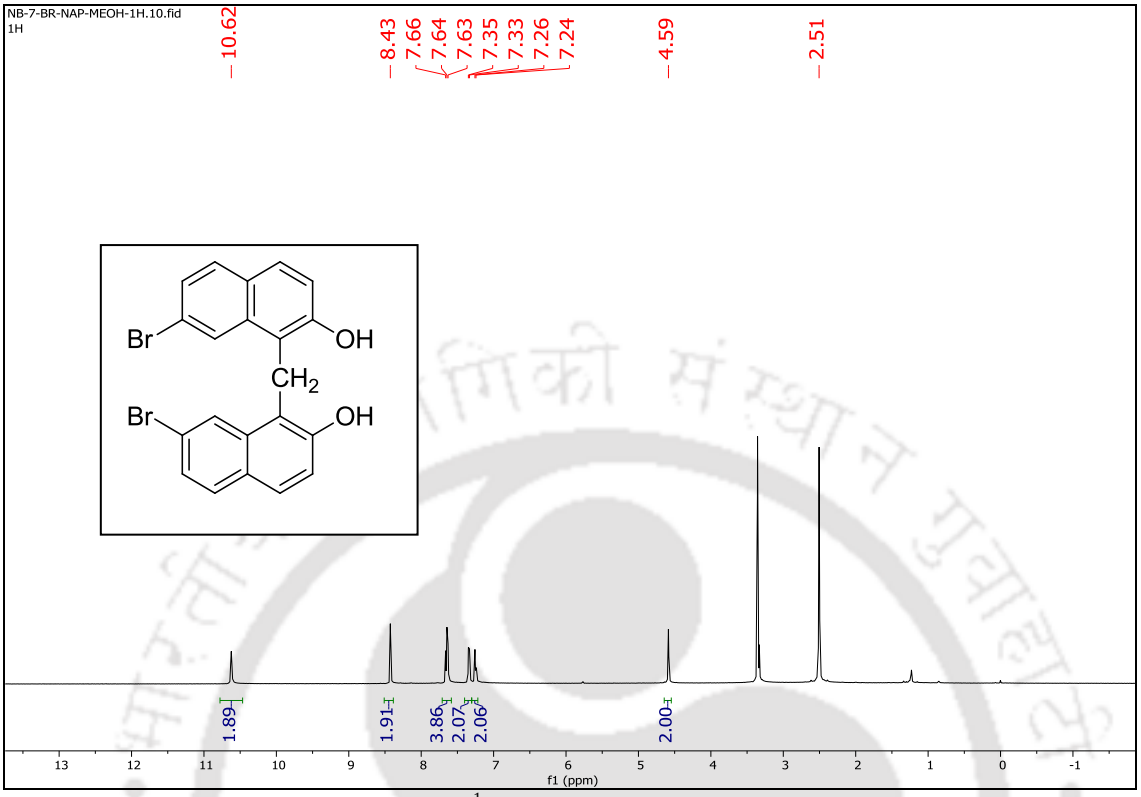

Figure 5.13: ^{1}H spectra of **5.8e** in DMSO-D_6

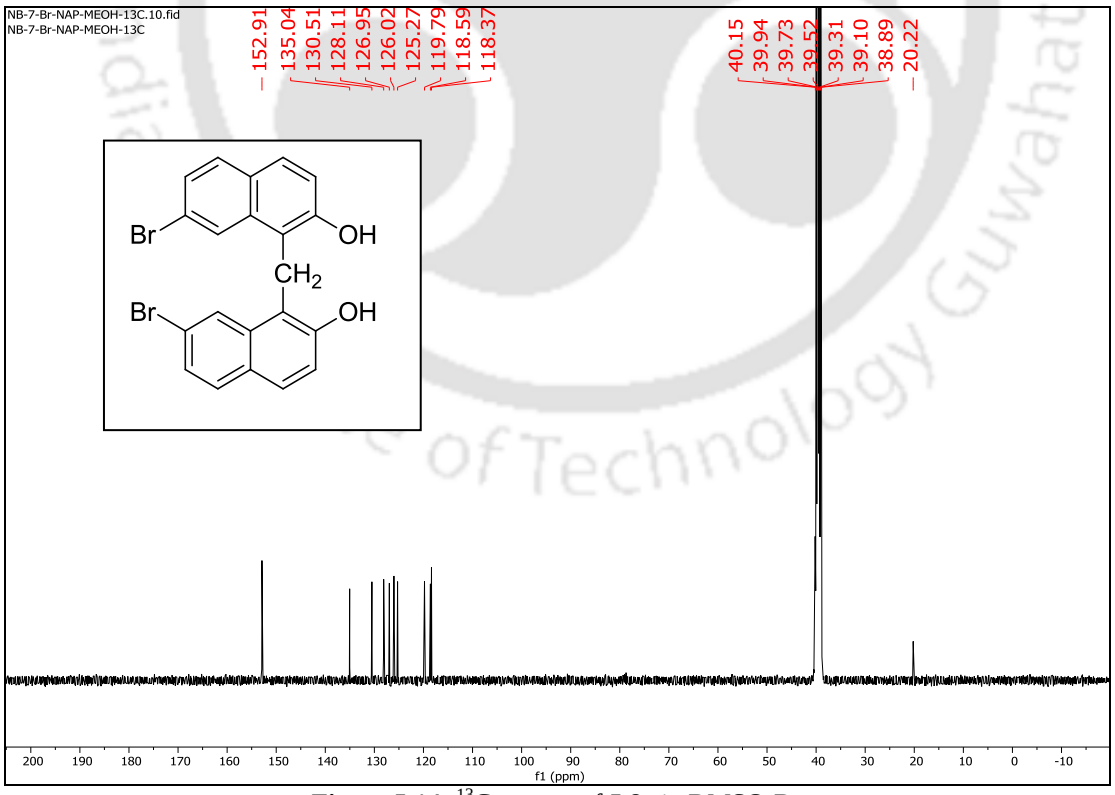

Figure 5.14: ^{13}C spectra of **5.8e** in DMSO-D_6

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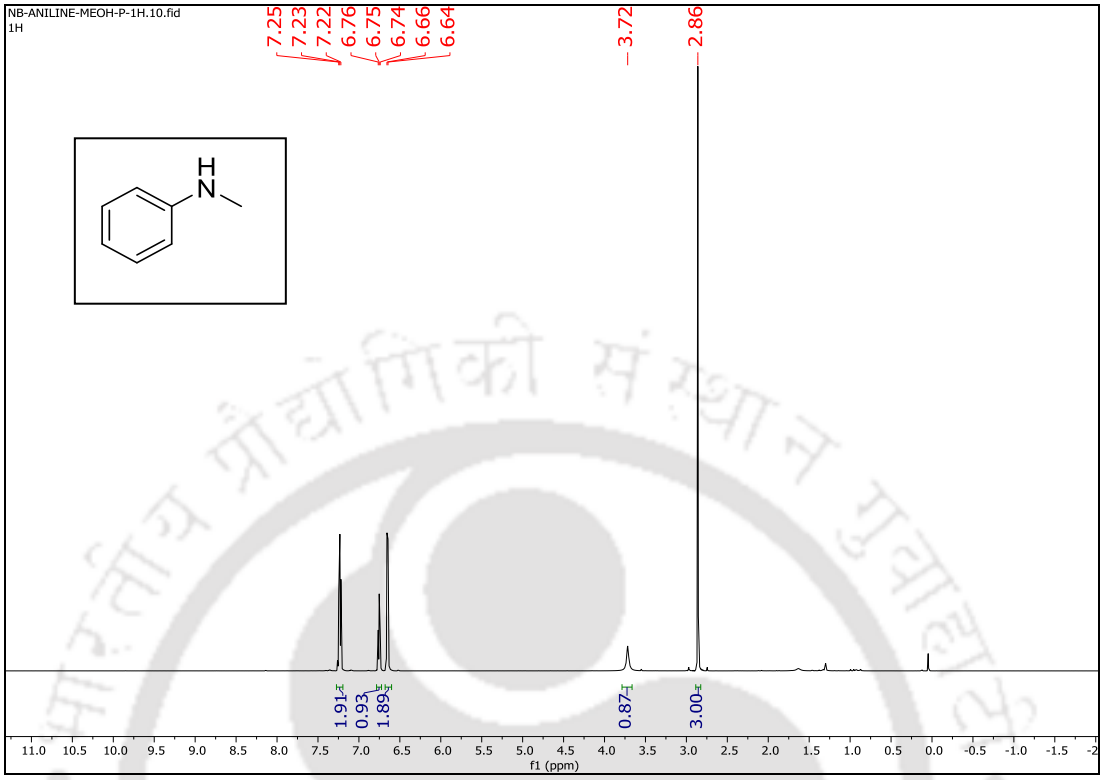

Figure 5.15: ^{1}H spectra of **5.10a** in $CDCl_3$

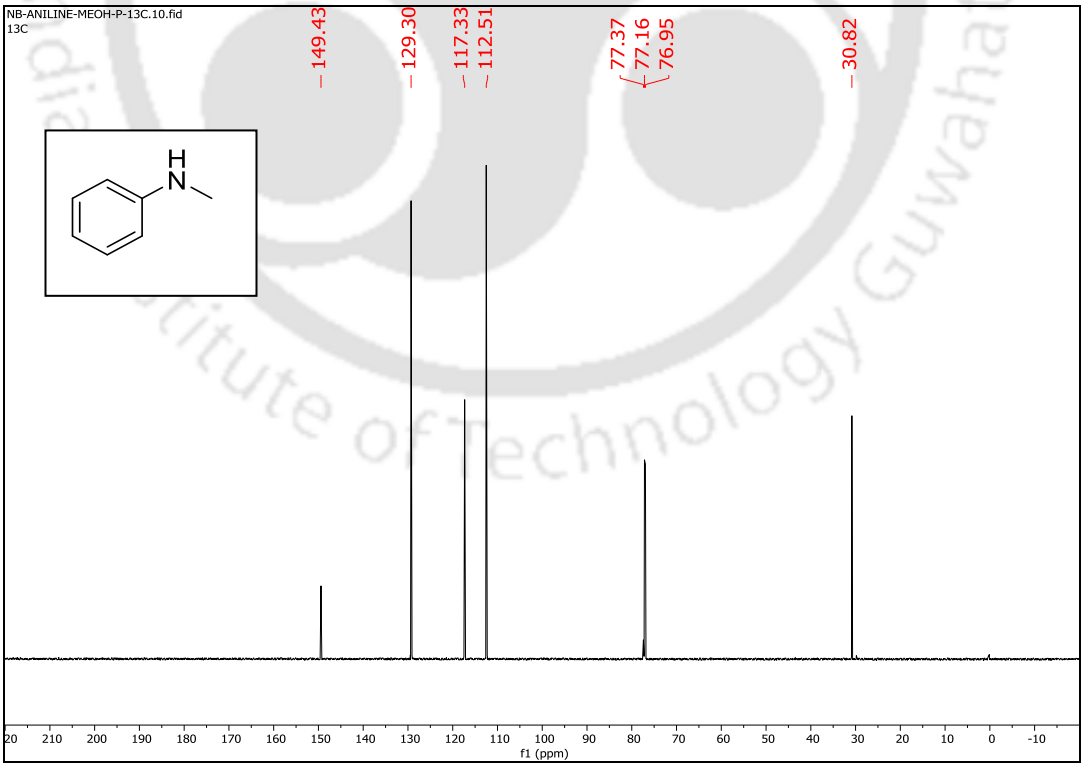

Figure 5.16: ^{13}C spectra of **5.10a** in $CDCl_3$

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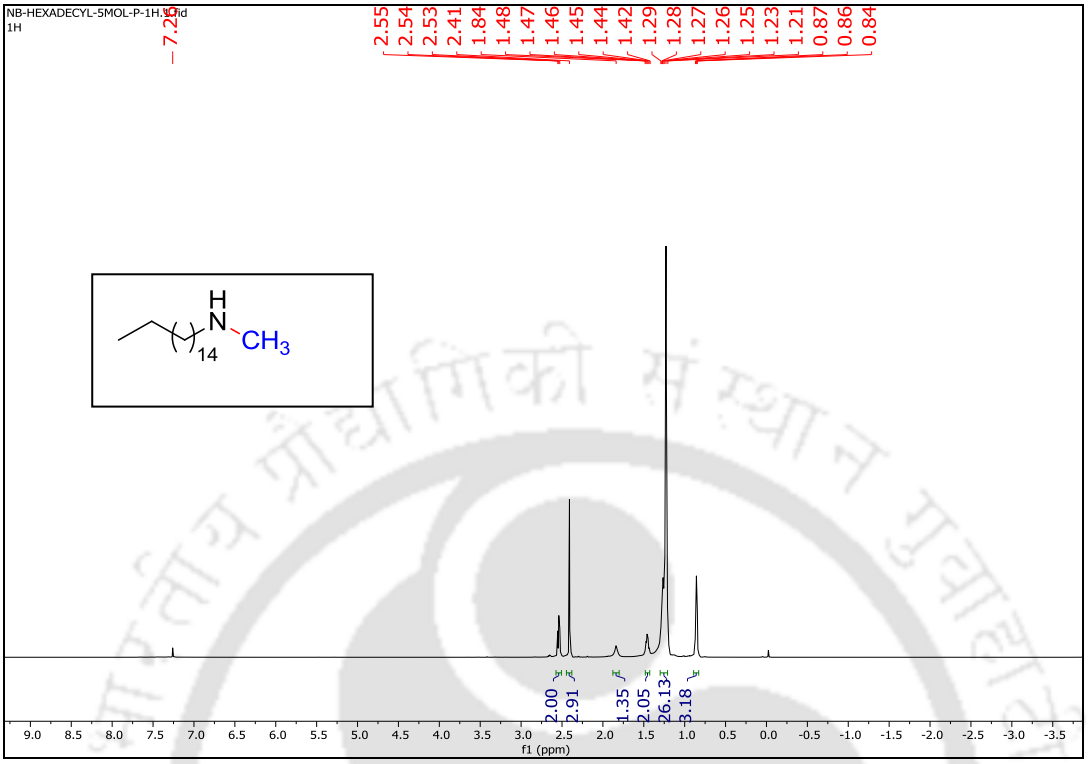

Figure 5.17: ^{1}H spectra of **5.10o** in $CDCl_3$

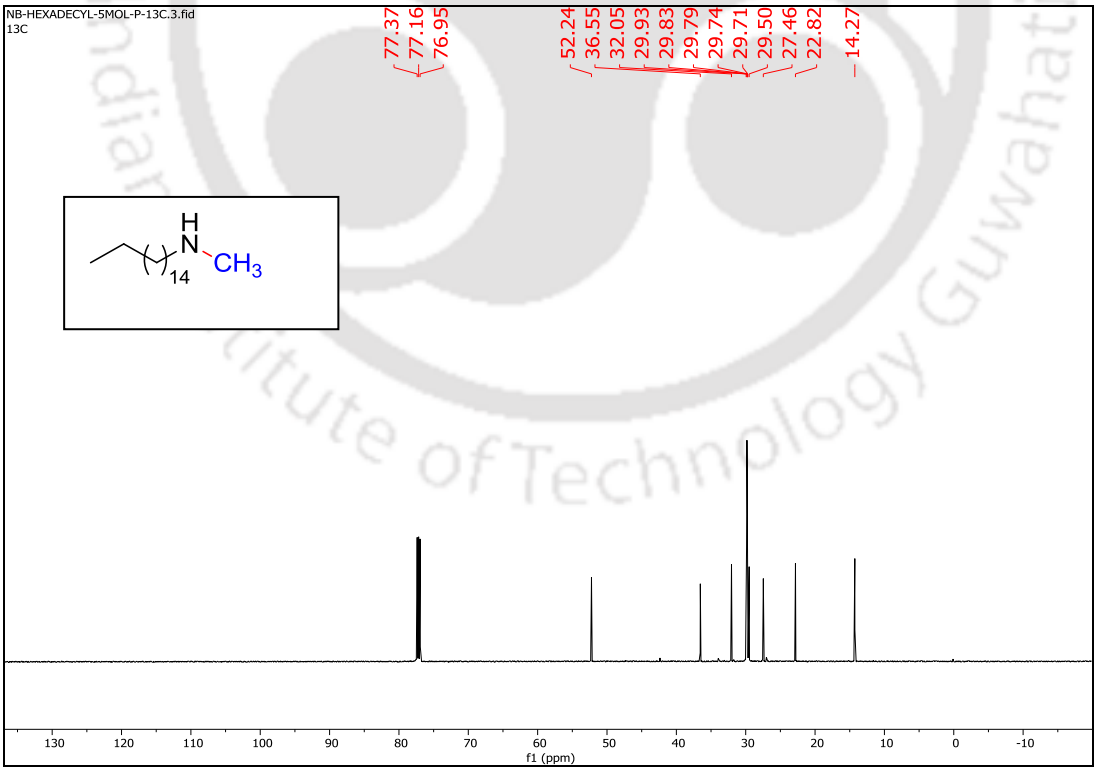

Figure 5.18: $^{13}C\{^{1}H\}$ spectra of **5.10o** in $CDCl_3$

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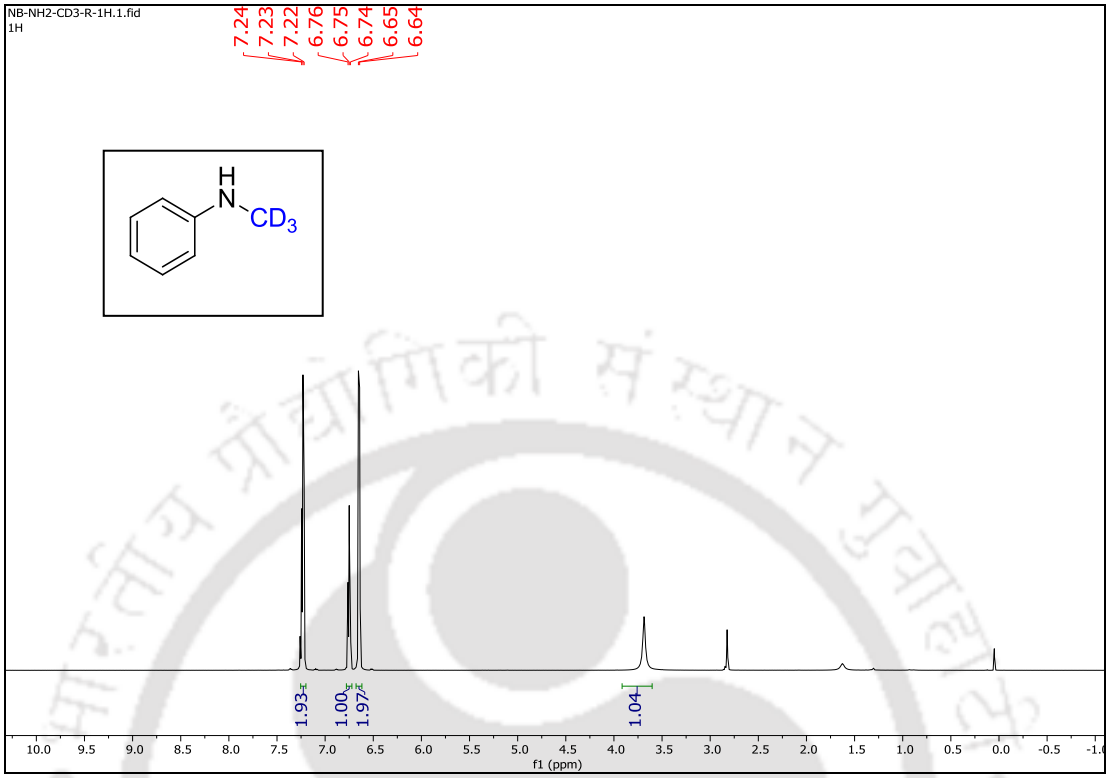

Figure 5.19: ^{1}H spectra of **5.10q** in $CDCl_3$

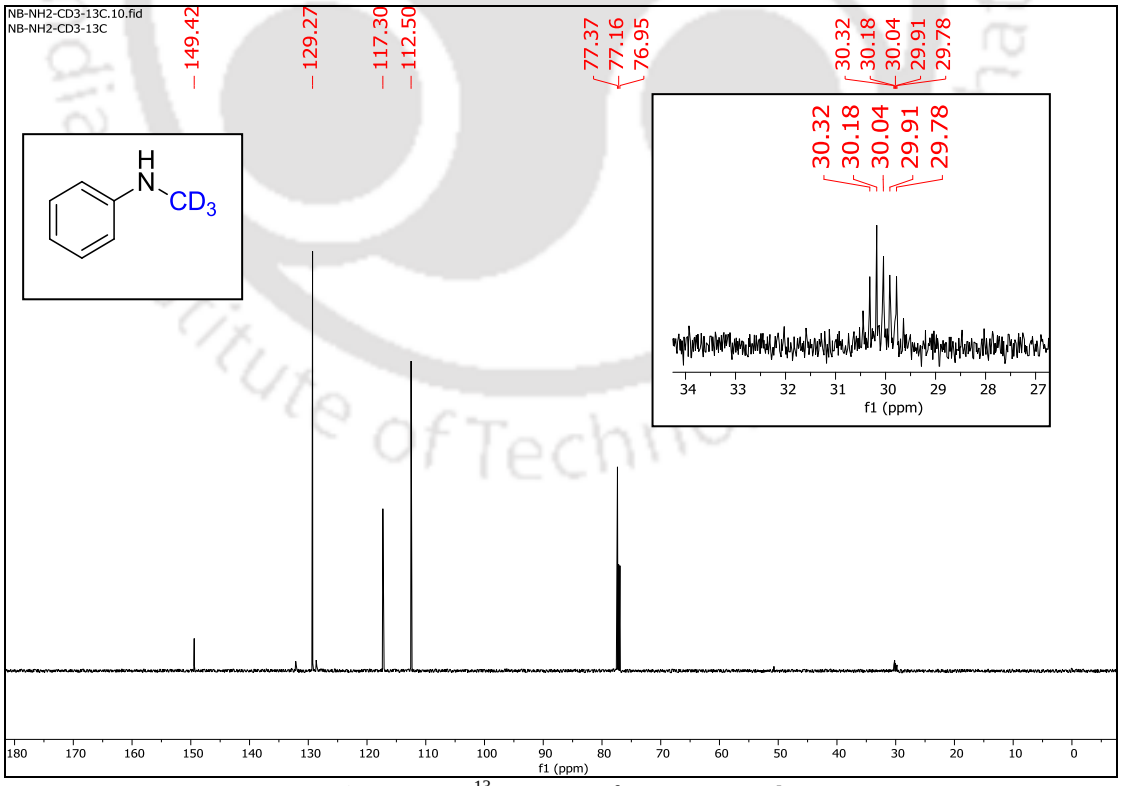

Figure 5.20: ^{13}C spectra of **5.10q** in $CDCl_3$

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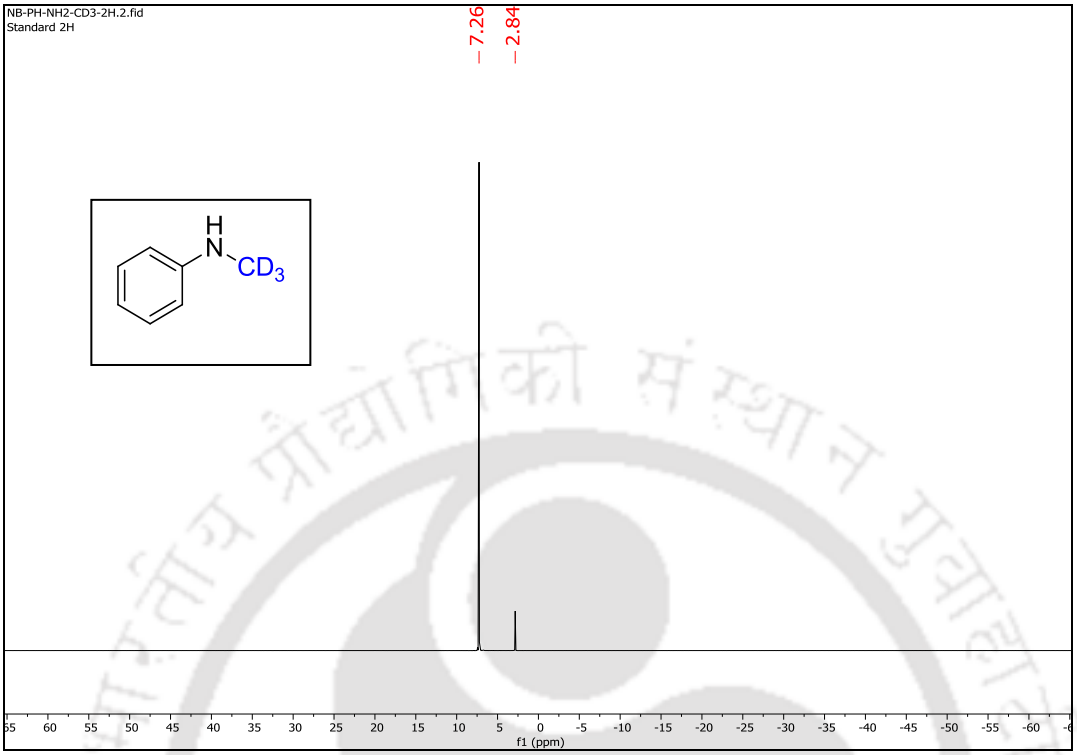

Figure 5.21: ^{2}H spectra of **5.10n** in $CDCl_3$

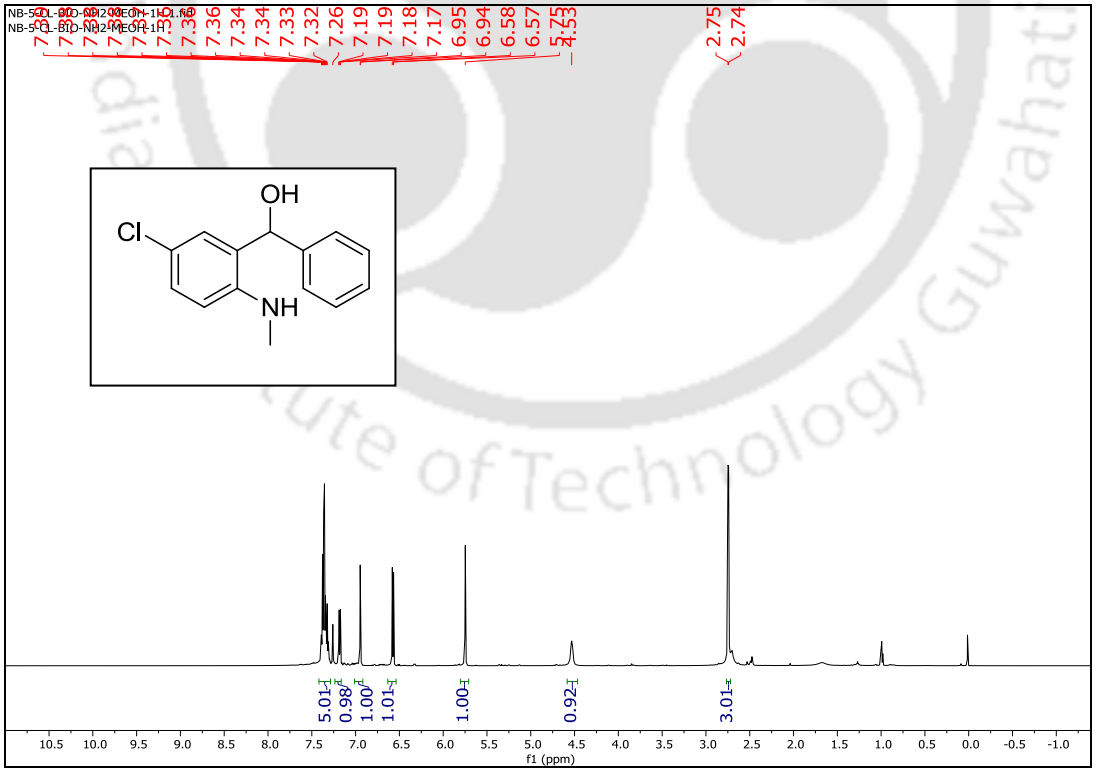

Figure 5.22: ^{1}H spectra of **5.10p** in $CDCl_3$

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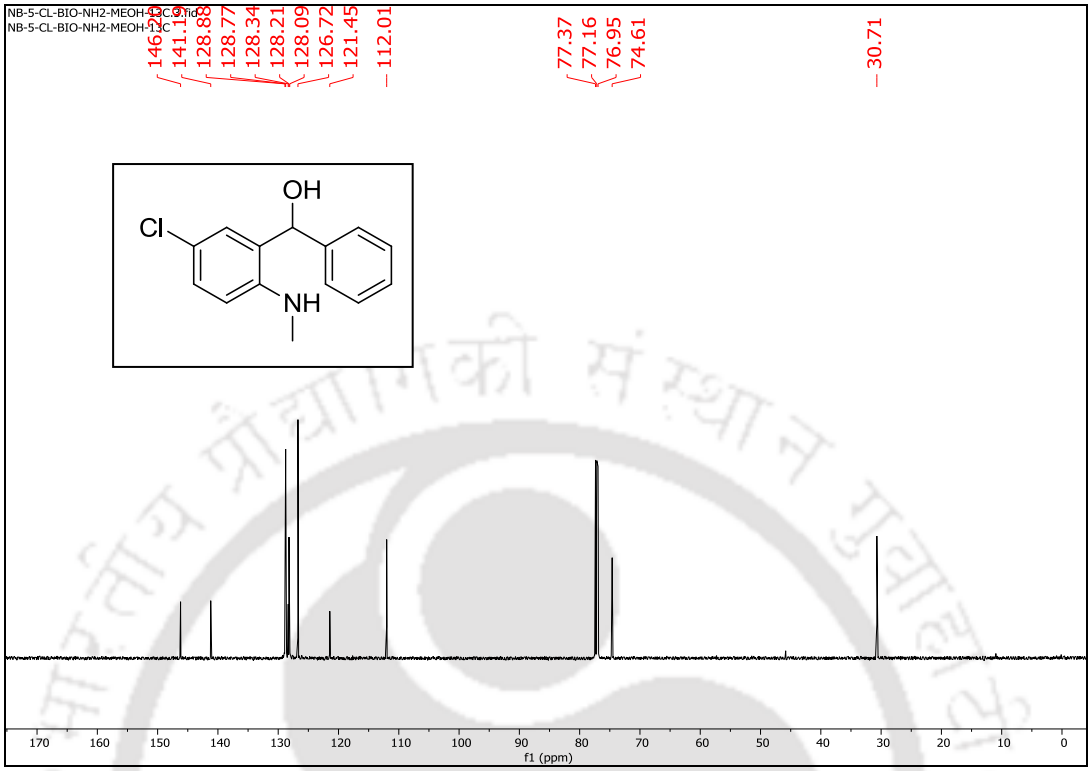

Figure 5.23: ^{13}C spectra of **5.10p** in $CDCl_3$

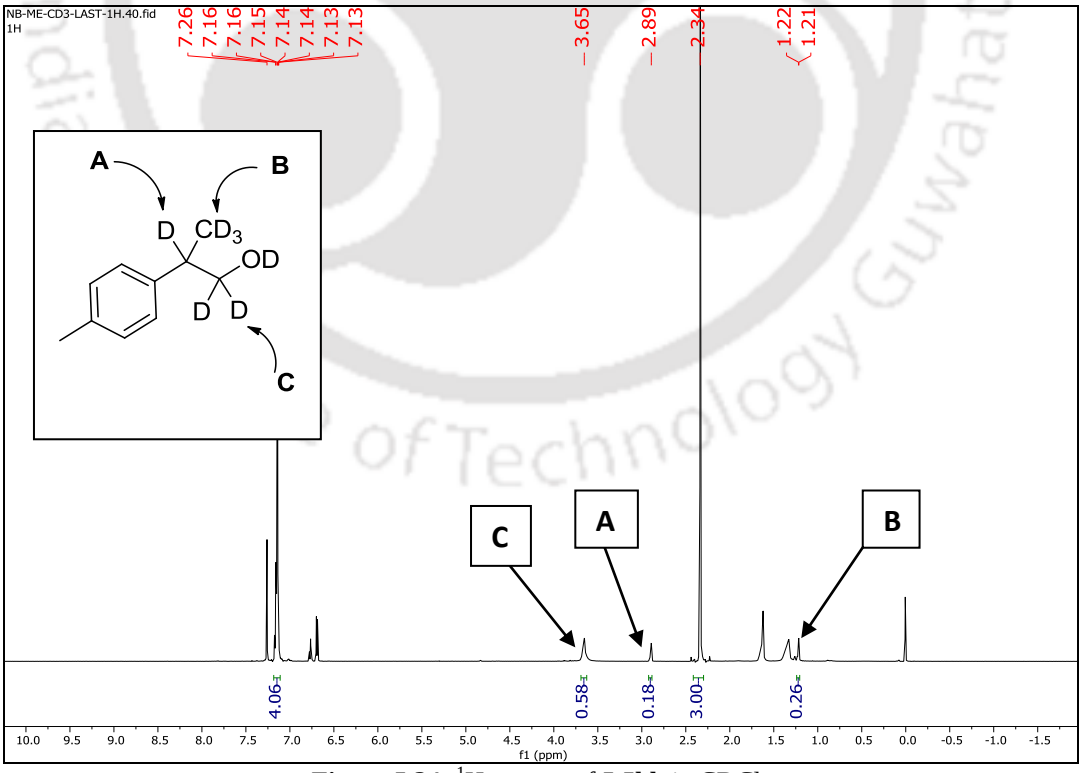

Figure 5.24: ^{1}H spectra of **5.5bb** in $CDCl_3$

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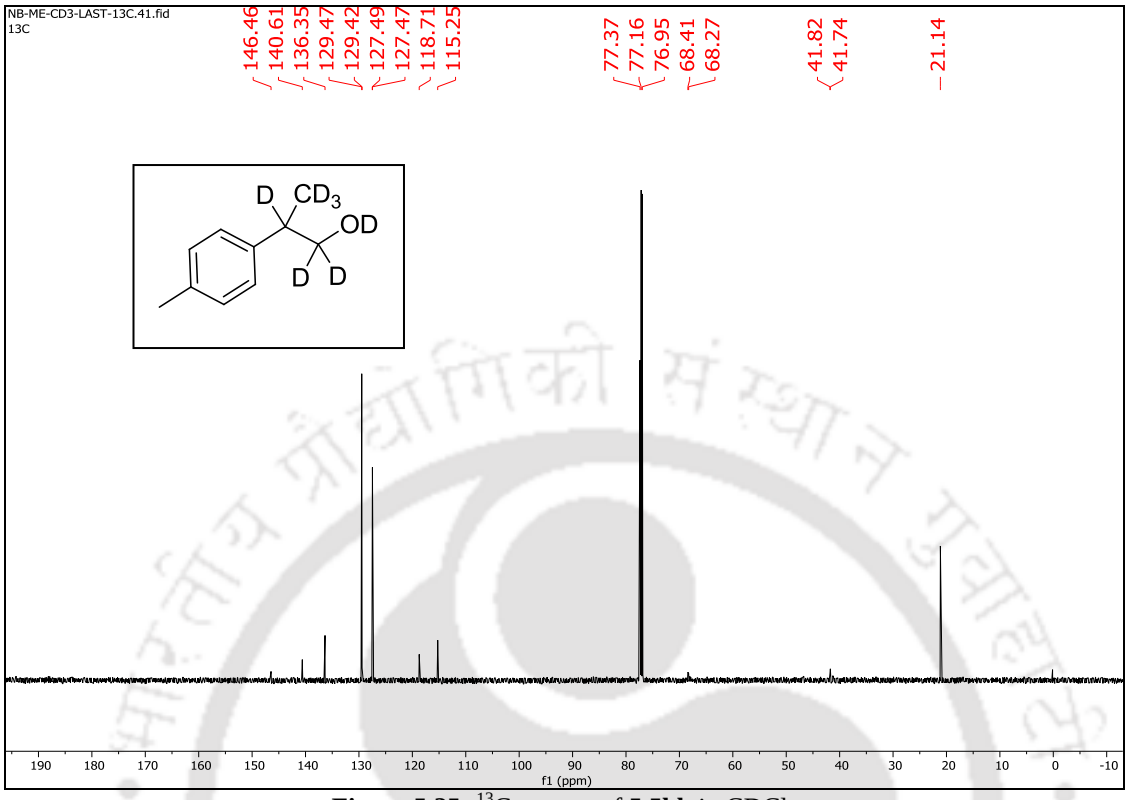

Figure 5.25: ^{13}C spectra of **5.5bb** in $CDCl_3$

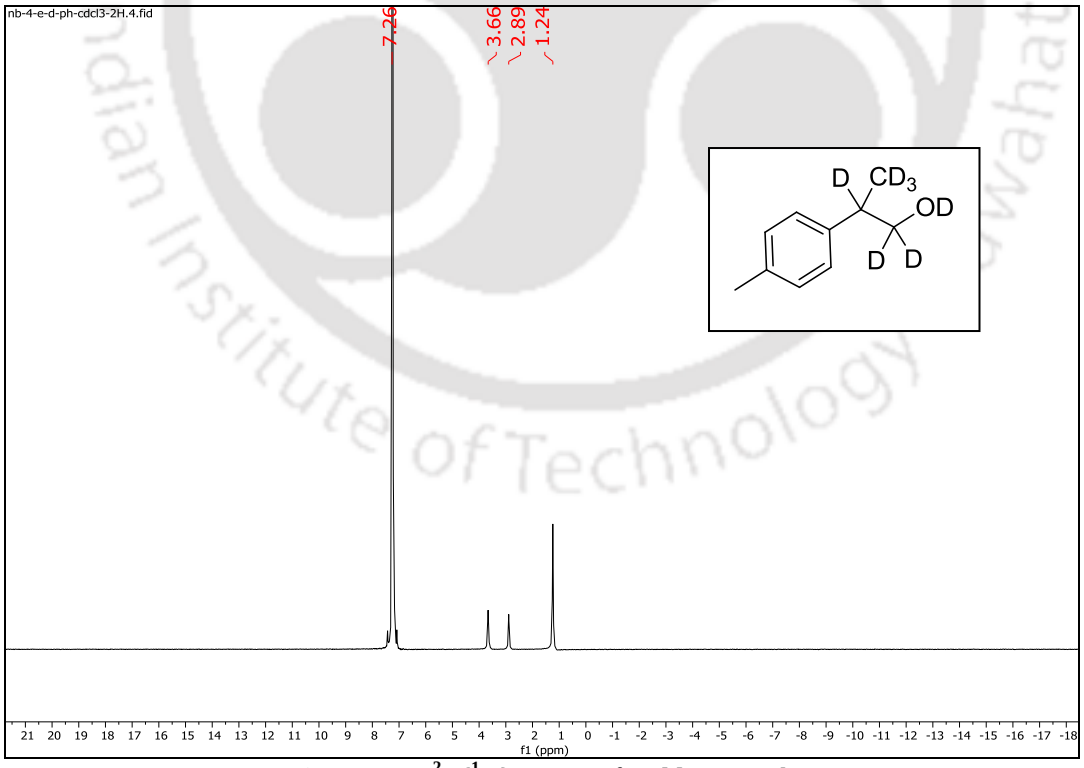

Figure 5.26: $^{2}D\{^{1}H\}$ spectra of **5.5bb** in $CDCl_3$

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Deuterium incorporation equation for the *β*-methylation of 2-aryllethanol.

% D = 100-((peak integral/equivalent protons)*100)

Peak **A**: 100-((0.18/1)*100) = 82% D

Peak **B**: 100-((0.26/3)*100) = 99.91% D

Peak **C**: 100-((0.58/2)*100) = 71% D

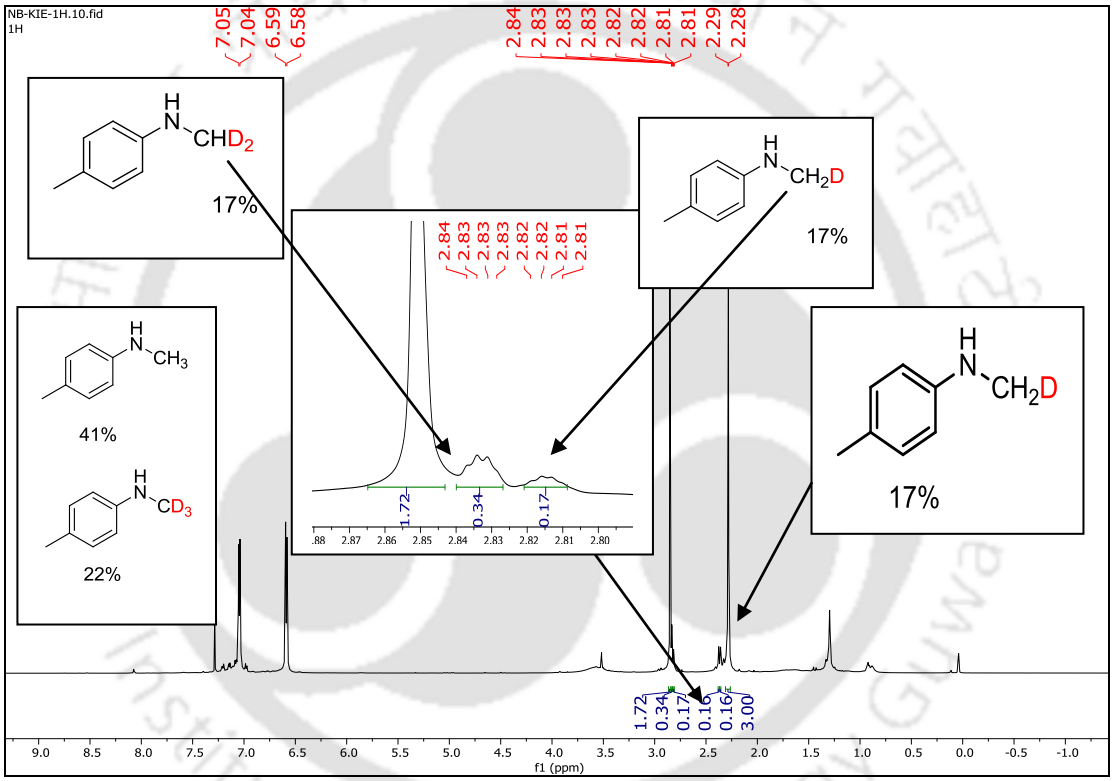

Figure 5.27: ^{1}H spectra of KIE experiment in $CDCl_3$ (in 600 MHz)

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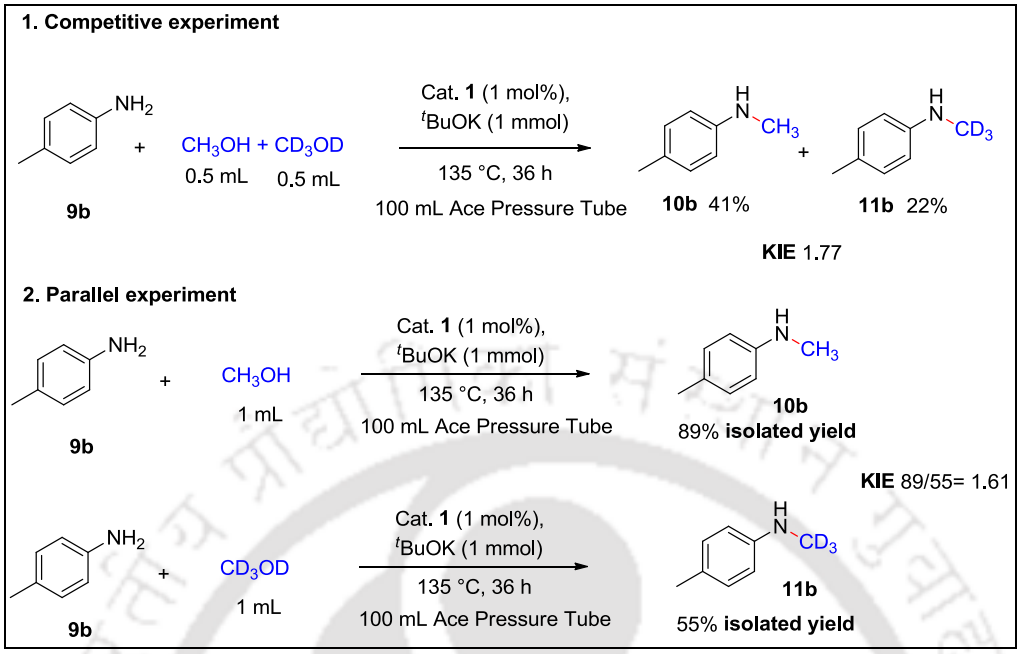

Figure 5.28: Labelling experiments with deuterated methanol and KIE calculation

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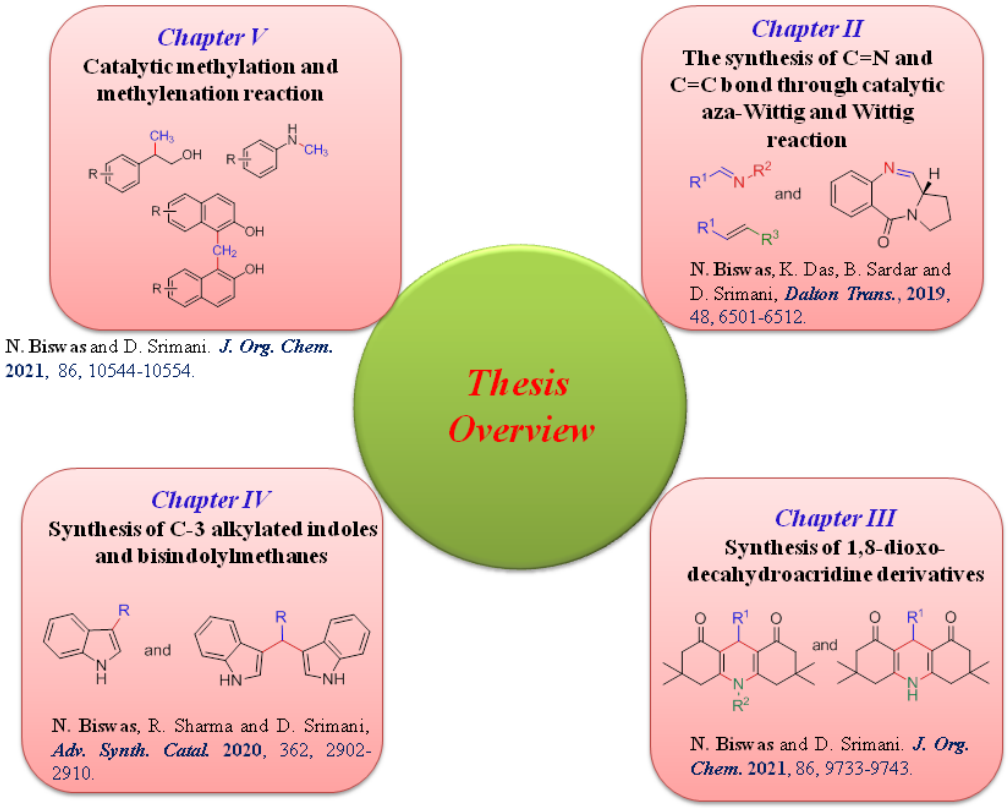

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Curriculum vitae

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Google Scholar Citation: https://scholar.google.com/citations?user=SdBYoEsAAAAJ

Personal information

1. **Date of Birth:** 15th January, 1992
2. **Place of Birth:** Madarihat, Alipurduar district, West Bengal, India
3. **Languages known:** Bengali, Hindi, English
4. **Marital Status:** Unmarried
5. **Hobbies:** Singing, Travelling, Reading.

Academic background

- **Thesis Title:** "Catalytic applicability of NNS and SNS ligand derived air-stable Ru complexes towards de(hydrogenative) construction of carbon-carbon and carbon-nitrogen bond"
- **Ph. D. July 2016-Present:** Indian Institute of Technology Guwahati (IITG), Assam, India. Supervisor: Dr. Dipankar Srimani
- **M. Sc. 2012-2014:** University of North Bengal, West Bengal, India. (**77.25**%)
- **B. Sc. 2009-2012:** Ananda Chandra College, West Bengal, India. (**63.25**%)
- **HS 2007-2009:** Kamakhyaguri High School, West Bengal, India. (**83.80**%)
- **10th 2007:** Nirobala Smriti Girls High School, West Bengal, India. (**85.63**%)

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Other Achievements

1. Qualified GATE examination in February, **2014**.
2. Qualified UGC NET examination in June, **2015**.
3. MHRD Fellowship for doctoral Studies in June, **2016**.

Doctoral research area

Design and synthesis of new pincer complexes and their application towards (de)hydrogenation and borrowing hydrogen reaction for making biologically important building blocks.

Research skills

1. Designing and synthesis of pincer complex.
2. Gathered depth knowledge in sensitive synthetic methodologies by using Schlenk line technique and Glove Box (Jacomax).
3. Experiences with High pressure catalytic hydrogenation reaction by using PARR instrument.
4. Operating NMR instrument (Bruker 600 MHz) for 1D and 2D NMR experiments.
5. Single crystal X-ray data solving by using XShell software package.
6. Skills in basic spectroscopic techniques including FTIR spectroscopy.
7. Mass spectrometric analysis.
8. HPLC, GC.
9. Knowledge in software including- Microsoft office, ChemDraw, MestReNova, Origine, Adobe Photoshop, Excell etc.

Other experiences:

1. Departmental Teaching Assistantship for practical responsibilities to guide B.Tech 1st year students in the Department of chemistry, IIT Guwahati since August, 2017. Also managing research laboratory and guiding bachelor's and master's student in his/her project in DS Laboratory since August, 2016.

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2. 4 years experience in operating NMR instrument (Bruker 600 MHz) for 1D and 2D NMR experiments.

3. Working as a guest lecturer at ***Kamakhyaguri Saheed Kshudiram College*** from September **2015** to April **2016**

M.Sc. Project work:

‘‘Green reduction of Graphene oxide using plant leaf extract of *Volvariclla volvacca* (mushroom)” submitted by **Nandita Biswas** semester-**IV**’2014 under the supervision of **Prof. Basudeb Basu** at Department of Chemistry, University of North Bengal.

Publications

1. Acceptorless dehydrogenative construction of C=N and C=C bonds through catalytic aza-Wittig and Wittig reactions in the presence of an air-stable ruthenium pincer complex.
   N. Biswas, K. Das, B. Sardar and D. Srimani, ***Dalton Trans.*, 2019**, 48, 6501-6512.

2. Ruthenium pincer complex catalyzed selective synthesis of C-3 alkylated indoles and bisindolylmethanes directly from indoles and alcohols.
   N. Biswas, R. Sharma and D. Srimani, ***Adv. Synth. Catal.* 2020**, 362, 2902-2910.

3. Synthesis of 1,8-dioxo-decahydroacridine derivatives *via* Ru-catalysed acceptorless dehydrogenative multicomponent reaction.
   N. Biswas and D. Srimani. ***J. Org. Chem.* 2021**, 86, 9733-9743.

4. Ru-catalyzed selective catalytic methylation and methylenation reaction employing methanol as C1 source.
   N. Biswas and D. Srimani. ***J. Org. Chem.* 2021**, 86, 10544-10554.

5. Ruthenium pincer catalysed Guerbet condensation reaction: An eco-friendly hydrogen borrowing strategy.
   N. Biswas, R. Sharma and D. Srimani. (Manuscript under preparation)

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List of conference/school/workshop participations

1. **Modern Trends in Chemistry and Chemistry Education** from 22nd to 23rd November, 2012, University of North Bengal, Siliguri: Participated.
2. **Frontiers in Chemistry** 28th February, 2013, University of North Bengal, Siliguri: Participated.
3. **Workshop in Diversities and Frontiers in chemistry** from 7th to 8th August, 2013, University of North Bengal, Siliguri: Participated.
4. **Frontiers in Chemistry**, 11th to 12th March, 2014, University of North Bengal, Siliguri: Participated.
5. **19th CRSI National Symposium in Chemistry** from 14th to 16th July, 2016: As a participant held in North Bengal University.
6. **ACS on campus** at IIT Guwahati 16th January, 2017: As an attendant.
7. **Frontier in Chemical Science (FICS 2018)** from 6th to 8th December 2018, Department of Chemistry, IIT Guwahati: **Poster** presentation with entitled *"Construction of C=N and C=C bond Directly from Alcohol through Catalytic Aza-Wittig and Wittig Reaction in the Presence of Air-stable Ruthenium Pincer Complex".*
8. **24th CRSI National Symposium in Chemistry and 13th CRSI-RSC Joint Symposium** from 8th to 10th February 2019: **Poster** presentation with entitled *"Construction of C=N and C=C bond Directly from Alcohol through Catalytic Aza-Wittig and Wittig Reaction in the Presence of Air-stable Ruthenium Pincer Complex*".
9. **Research Conclave 2019** from 14th to 17th March, 2019: **Poster** presentation with entitled *"Construction of C=N, C=C bond; formation of Indole and its functionalisation in one-pot, in the Presence of Air-stable Ruthenium SNS and NNS Pincer Complexes"*. **Awarded with 3rd Prize.**
10. **XV J-NOST Conference 2019** from 18th to 21st October, 2019: **Poster** presentation with entitled *"Ruthenium Pincer Complex Catalysed Acceptorless Dehydrogenation and Borrowing Hydrogen Catalysis: A Sustainable Approach to Synthesize Important Building Blocks".*

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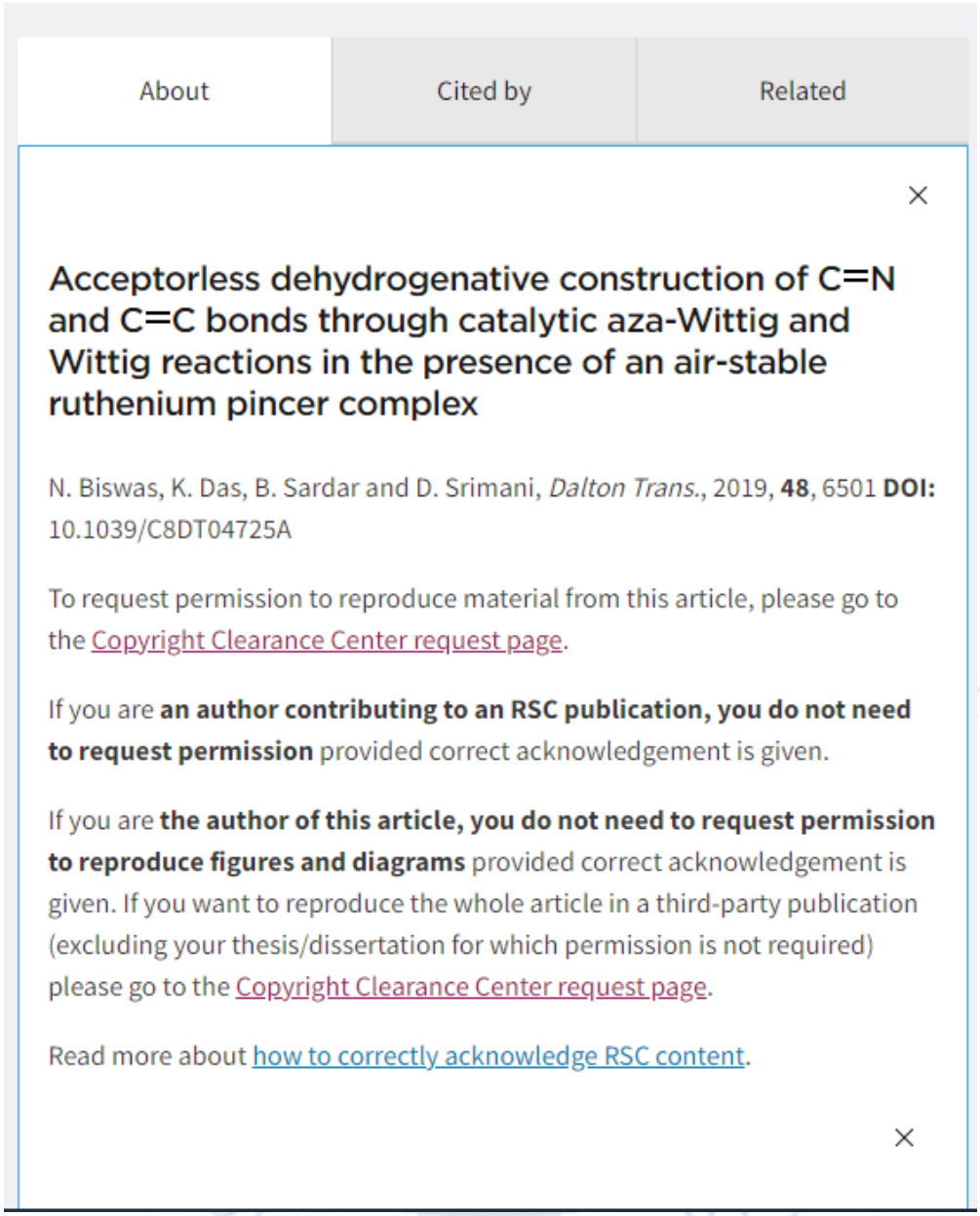

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Acceptorless dehydrogenative construction of C=N and C=C bonds through catalytic aza-Wittig and Wittig reactions in the presence of an air-stable ruthenium pincer complex

N. Biswas, K. Das, B. Sardar and D. Srimani, *Dalton Trans.*, 2019, **48**, 6501 **DOI:** 10.1039/C8DT04725A

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Synthesis of 1,8-Dioxo-decahydroacridine Derivatives via Ru-Catalyzed Acceptorless Dehydrogenative Multicomponent Reaction

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Title	Catalytic applicability of NNS and SNS ligand derived air-stable Ru complexes towards de(hydrogenative) construction of carbon-carbon and carbon-nitrogen bond
Institution name	IIT GUWAHATI
Expected presentation date	Aug 2021
Requestor Location	Ms. NANDITA BISWAS C-135, SUBANSIRI HOSTEL IIT GUWAHATI CAMPUS GUWAHATI, 781039 India Attn: Ms. NANDITA BISWAS
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